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RECENT ADVANCES IN DIABETIC THERAPY

ARTHUR A. HEROLD, JR., M. D.
SHREVEPORT

The title *Recent Advances in Diabetic Therapy* is an unfortunate one. Perhaps a better title would be *A Consideration of Some Therapeutic Approaches in Diabetes Mellitus.* Our progress in diabetic therapy since the discovery of insulin in 1922 has been slow and at times very discouraging. Frederic M. Allen's myrtillin,[1] an extract of blueberry leaves, did help to keep the adult diabetic in good condition. However, diet and insulin were required as basic treatment, and the product was of so little value in long range therapy that it was abandoned.

In 1927 the Nobel prize in medicine was awarded to Professor Frank of Breslau, Germany, for producing synthaline. This insulin substitute is a synthetic compound,[2] deca-methylene-diguanidine, which produces a considerable lowering of the blood sugar. Its use was discontinued because of the frequent severe gastric irritation which it caused. Neosynthaline, which does not cause so much gastric irritation, is unfortunately inert. We will dismiss the many yeast products for which extravagant claims have been made by simply saying that none of them have proved to be of any value. Some of the pancreatic extracts which are taken orally seem to be of considerable value. Panteric tablets are useful in the management of the mild diabetes that occurs in people past middle age, and their judicious use, in conjunction with a strict diet, and weight reduction if indicated, may be sufficient to avoid the use of insulin, except in times of surgery or infection.

In 1933, Joslin remarked that "The time is ripe for something new in the field of diabetic therapy." I suspect that he had been hearing from Copenhagen, for it was only a few months later that word was received from Hagedorn about protamine insulinate. The excitement caused by the announcement is a well remembered event. The newly modified insulin was hailed as the ultimate in insulin therapy, and there was talk of obtaining smooth, even control of blood sugars with the use of one or two doses of protamine zinc insulin weekly. Subsequent work revealed the true limitations of the drug, the failure of a morning dose to control glycosuria and hyperglycemia on the day of injection, and the distressing nocturnal hypoglycemia. The consensus of opinion today seems to be that the best type of one dose therapy for the average diabetic is the so-called "two-one mixture", that is, two parts of regular insulin combined with one part of protamine zinc insulin. In this respect I would like to say that the newest of the insulins, NPH-50, has, in our limited experience, been superior to the results observed with the two-one mixture. That is, we have observed a smoother curve, with a low fasting level and no untoward reactions. I regret that I do not have complete records on our ten

From the Medical Department of the North Louisiana Clinic, Shreveport, Louisiana.

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patients on NPH-50, but I would like to cite the results in one case.

M. A. G., a 12 year old girl, was first seen on November 30, 1949. At that time the urinalysis revealed 4 plus sugar and 2 plus acetone. Weight was 107 pounds. Fasting blood sugar on December 3, 1949 was 263 mgm. %. She was given an 1800 calorie diet and placed on 24 units of NPH-50 at 7:00 A. M. daily, with dramatic response. Blood sugar on December 26, 1949 was 78 mgm. %, following which the NPH-50 was reduced to 20 units at 7:00 A. M. On January 1, 1950, the blood sugar was 82 mgm. %. Repeated urine specimens at different times during the day have never had more than a trace of sugar, and best of all, the child has not had a single severe episode of hypoglycemia. Results as good as these in juvenile diabetics with other types of insulin have been unusual in our experience, even with multiple daily injections.

Priscilla White[3] reported that in 95 per cent of 336 persons with severe diabetes, modified protamine insulin was used as successfully as, if not more so, than separate injections of crystalline insulin and protamine zinc insulin. H. T. Ricketts,[4] of Chicago, in commenting on the new insulins said, "NPH-50 is still not an ideal insulin, but the day of the ideal insulin is not at hand. Meanwhile, there is little point in continuing a preparation—protamine zinc insulin—which has to be hand mixed with another for the single dose management of persons with severe diabetes, if a more effective manufactured preparation, satisfactory for the vast majority of patients and capable of further modification when necessary, can be made available."

A recent communication from Dr. Peck,[5] of Eli Lilly & Company, states that the drug will be available on a commercial basis in the next few months.

The second improvement in insulin therapy is a combination of insulins about which I have been able to find but a single reference in the literature.

I refer to a combination of regular insulin and globin insulin,[6] given twice daily, preferably before the morning and evening meals. The uses of this combination are limited to: (1) Those diabetics who for one reason or another cannot take or cannot tolerate protamine insulin; (2) those diabetics whose disease is so severe that they require multiple injections for adequate control; and (3) those diabetics with surgical or obstetrical conditions who should be under strict twenty-four hour control. For the last of these conditions the New England Deaconess group[3] uses, "Separate injections of crystalline and protamine zinc insulin before breakfast, supplemented by crystalline insulin before lunch, dinner, and even at bedtime." In theory this is satisfactory, but in actual practice nearly all the patients will object to the frequent injections, and the priceless cooperation of the patient may be lost. In my experience a three-one mixture twice daily gives the maximum in twenty-four hour control. Thus, a diabetic requiring 80 units of insulin daily and falling into one of the three aforementioned categories, would receive 30 units of regular insulin and 10 units of globin insulin before the morning and evening meals.

I recently saw a young adult diabetic who falls into this category. He had always had fasting morning blood sugars in the range of 250 to 400 mgm. % on two doses of plain insulin, given before breakfast and supper. He also did very poorly on protamine zinc insulin by itself and in various combinations with regular insulin. At 5:00 P. M. in my office he complained of nervousness and had a blood sugar of 56 mgm. %. In for a check-up a week later, the fasting blood sugar at 7:30 A. M., thirteen hours after the last dose of insulin, was 70 mgm. %, and he felt well. At noon he was nervous, and had 47 mgm. % of sugar. He was instructed to eat a meal very high in carbohydrate content, and at 4:30 P. M. the blood sugar was 187 mgm. %. This patient's carbohydrate tolerance has improved steadily, and from a high of 115 units his dosage has been reduced to a daily total of 70 units. The main precautions with this combination are midmorning and bedtime meals, to avoid midday and early morning hypoglycemia.

The third improvement in therapy is one that at the present time is unfortunately more apparent than real. I say this because it is obviously an improvement but at

the present time is not available anywhere other than at a few research centers. I refer, of course, to the hypospray, the so-called "Jet injector." This instrument was to have been on the commercial market this spring, but a recent communication from Mr. J. M. McKibbin,[7] director of research for the Scherer Corporation, informed me that the instrument probably will not be marketed before June of 1951. The main difficulty is the price, which at present is prohibitive.

There are many who doubt the value of the instrument. Lawrence[8] states that he, "Prefers an almost painless prick to a noisy blow from a hammer." Nevertheless, its value as an aid to absorption is undeniable. The distribution of the dose in microscopic amounts over a 3 cm. area, and the ability to utilize sites such as the abdominal wall, which are often painful on needle injection, assure a sharp decrease in the incidence of the painful and disfiguring insulin lipodystrophy. This unfortunate sequel of repeated injections of a highly acid substance into a localized area will apparently be a thing of the past once the cost of the injector becomes reasonable.

I have presented three modest but distinct improvements in diabetic therapy. What will come next we cannot say, but a better understanding of the endocrine interrelationship of the pituitary, adrenal, thyroid, and pancreas is basic before we can hope to offer more than replacement therapy. In this respect the recent work on the adrenocorticotropic hormone seems to be a large step in the right direction, and offers hope for new major advances in the not too far distant future.

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THE RATIONAL TREATMENT OF DIABETES MELLITUS AND DIABETIC COMA

MANUEL GARDBERG, M. D.
NEW ORLEANS

It is the purpose of this paper to discuss the treatment of diabetes mellitus and diabetic coma from the point of view of the practice of medicine. The necessity for this statement of orientation is created by the too common confusion of investigative or scientific medicine with clinical practice, a confusion which benefits neither the one nor the other and the patient least of all. The clinician, whose interest is primarily the welfare of the individual patient, and not investigation of the disease, is anxious to apply any scientifically established fact to the welfare of his patient and to that end must be cognizant of advances in the scientific field. However, the "advances" frequently represent only theoretical speculation on the part of the scientist who has presented it with one or two points of support, sufficient to lend the speculation plausibility but insufficient to establish it as fact. The clinician (and scientist as well) who imbibes too avidly the enormous volume of scientific literature presently available frequently confuses plausibility with truth, and therefore, fails to distinguish between speculation and established fact, and attempts to apply the so-called advance as though it were fact.

It is true that much of medical practice necessarily rests upon speculative basis for in many problems little of proven fact is available. However, wherever it occurs in medicine, the speculative or theoretical basis of therapy must be evaluated as such so that it will not take precedence over or preclude some basis for action which conflicts with it and which is indeed a matter of proven fact. The treatment of diabetes

From the Department of Medicine of the Louisiana State University School of Medicine and the Medical Departments of the Charity Hospital and Touro Infirmary at New Orleans.

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mellitus bears some discussion from this point of view.

Early in the history of diabetes mellitus attempts were made to relate glycosuria to the development of early arteriosclerosis and other complications in the diabetic. There has never been any final proof that this is actually so. Many have pointed out that some diabetics who have taken only a desultory care of their diabetes do not exhibit early arteriosclerosis, while others who have been quite meticulous in this regard suffer this complication to an inordinate degree. On the other hand, others who have attempted to study the problem state that there is a statistically significant difference between the incidence of complications in the two groups. This statistical evidence does not seem to be imposing. Thus the fact remains that the idea that hyperglycemia and glycosuria account for the vascular complications of diabetes mellitus still remains on a speculative basis where it began years ago. Yet in many quarters this idea is accepted as fact and is employed as a strong basis for action, i.e., therapy.

As a result of the application of this principle it is demanded that the urine be kept sugar free and often that the blood sugar be kept below hyperglycemic levels during the twenty-four hours of the day. This objective can be gained only with a great deal of difficulty—for the patient, and has far reaching, often tragic consequences. It means *rigid* adherence to a diet, rigid timing of insulin doses, often a rigid schedule of exercise and activity; matters which come into conflict almost daily with the patient's normal way of life. The rigid regime may be enjoyed by a few self-centered obsessives, but the impact of these things upon most persons is very depressing and demoralizing; it constitutes a species of imprisonment of their liberties while at the same time constituting a continuous reminder that they are sick and not like other people. Most patients rebel against the psychological effects of the rigid regime and will conform only if they are strongly impressed with the idea that dire consequences will follow upon infraction of the rules. They are made to conform through fear and they live the rest of their lives in fear. Bolder spirits are apt to throw the whole regime overboard except for the insulin and live their normal lives under the philosophy that "while they live they might as well really live." Others, finally, are in an intermediary group, remaining somewhat fearful only of the physician as a symbol of the threats he has made, "breaking training" between visits but going back into training a few days before each check-up so that their specimens will be clear of sugar and their fasting blood sugars low. The physician is in many instances deceived and the patient accepts his good report with all the air of virtue of a small boy who has just "put one over."

I am certain that living in fear and conflict is not healthful. I am certain that the emotional effects of making the diabetic feel so different from other persons, and so constantly conscious of the idea that he is sick is not healthful, does not lengthen but shortens his life. The effects upon children in the formative years of the personality are even more devastating than in adults. These are not matters of speculation, they are matters of indisputable observed fact. I am certain that the rebellious diabetic who is in constant conflict between his rebellion and the fears which have been instilled into him cannot help but suffer from the tension produced by this conflict, and since he frequently jumps the traces and does as he pleases even the advocates of rigid control can hardly approve of the results in such cases.

It is my thesis that these positive hazards should not be incurred as a result of adherence to the very questionable speculation that arteriosclerosis in the diabetic is hastened by hyperglycemia and glycosuria.

METHOD OF MANAGEMENT

The diabetic should be impressed, first of all, with the idea that the disorder is compatible with normal life, that the diabetes should have little effect upon his way of living and that there is no reason why it should change the way he thinks and feels about himself and his life, including his life

expectation. A bit of care of the diet, which today is a normal full diet except in the obese, and a dose or two of insulin a day, which after all is not nearly as much trouble as shaving, and things remain the same insofar as the pursuit of life, liberty, and happiness is concerned. It is true that his liberty is curtailed to the extent that he may not indulge himself *freely* in quantities of food and sweets. It is just as well to point out the fact that this curtailment is necessary to prevent him from becoming obese, for even with the moderate control of glycosuria which I have practiced the patient will become obese if he over indulges. The patient is not hospitalized for stabilization for the several reasons that (a) it is unnecessary where no complications exist, (b) it violates the above mentioned policy of psychological management, and (c) it is too often necessary to repeat the whole process of stabilization upon discharge from the hospital because of the differences between hospital and active life.

A diet of 1500 calories is prescribed routinely in every case except in the obese patient who is given 1000 calories. This diet is prescribed in the form of a master menu expressed in household quantities. For each item on this menu a list of quantitative substitutions is furnished so that the patient may vary the menu at will without difficulty. The advantage of this simplified method resides in the fact that it makes it unnecessary for the patient to make any sort of calculations.

Four specimens of urine are collected daily. These are obtained before each meal and at bedtime and are examined with Benedict's qualitative solution, a procedure which the patient is taught early. If the sugar disappears from all specimens within a week the patient may need no insulin. If the specimens give red, orange, and yellow reactions over a period of four or five days, insulin should be begun.

Time does not permit a full discussion of insulin dosage. Suffice it here to say that the dose is determined purely by trial and error, using the four specimens as a guide. One usually begins with 10 or 15 units of protamine zinc insulin, adding one glass of milk and three crackers at bedtime to the diet to avoid early morning reactions. The dose is increased every fourth day by 5 to 10 units until the four specimens give satisfactory tests or until it is clear that one dose of PZI will not suffice without producing a reaction. The specimens are considered satisfactory if three out of the four show no more than a trace of sugar. If PZI alone will not give adequate control, one tries one of the mixtures of PZI and regular insulin. They will do anything that globin insulin will do and more. If the single dose of a mixture does not suffice and two doses of insulin become necessary, most cases will do better with two doses of regular insulin, one-half hour before breakfast and one-half hour before supper, than with any other arrangement. The flexibility of this latter arrangement is an additional advantage to the patient. The patient learns easily to change the proper dose of insulin when anything unusual happens and over a long period of time keeps his diabetes in better control and at the same time feels more independent with the high degree of self-management possible under these circumstances.

The patient learns the diet in terms of household quantities, so that if he has dinner out he will be able to approximate what he should have. He is advised as to how to avoid reactions if meals are delayed—as at banquets. He is taught that an occasional drink or irregularity in the diet will not kill him and that if the "bad" specimens thus produced (most often they are not) clear up in another twenty-four hours, no harm has been done. Otherwise he is advised to examine the four specimens on one day a week and then to forget about them.

This method of management will bring at least as good results as the method of rigid control insofar as complications are concerned. It will bring tremendously greater results in terms of happiness and general well being. Its simplicity is its truth and its principle.

DIABETIC COMA

In diabetic coma therapy, often there is

much preoccupation with the methods of research medicine which are as yet not easily applicable to practice. In persons in diabetic coma the scientists have studied the behavior of the blood sugar, the nonprotein nitrogen of the blood, the blood chlorides, the total base and the blood potassium, and we have learned from these studies some things about the treatment of diabetic coma. However, the idea that estimations of these values are to be used in the proper treatment of every individual case of diabetic coma is erroneous. While they have been of inestimable value in teaching us more about the physiology of diabetic acidosis, these procedures are of little value in the treatment of diabetic coma in practice for the following reasons that: (a) They are not available to us; for not even in the larger hospitals in the large cities can one obtain these estimations at the half hourly or hourly intervals that might make them of some use. (b) These estimations are estimations of concentrations only, and not of total quantity within the body. In diabetic coma the latter is the important thing for consideration, and no accurate estimation of total quantity in this condition is possible because we have no accurate way of measuring the degree of dehydration which, moreover, is constantly changing under treatment. Finally, these estimations are largely unnecessary to the treatment of diabetic acidosis. It is necessary only to employ the knowledge gained through them by the scientist.

One can get a satisfactory estimation of the degree of dehydration of the patient simply by looking at his tongue. One can known from the research studies mentioned above that there is in diabetic coma a diminution of total base, of chloride, and of bicarbonate, and that blood potassium may be low although it should not be treated until rehydration has been effected. Treatment is directed against these things, shock, and dilatation of the stomach, as well as the insulin need. Treatment, then, should consist of the use of large doses of insulin, large volumes of intravenous fluid, chloride, and occasionally sodium lactate or even bicarbonate in severe cases. Glucose is used to "cover" the large doses of insulin which should be given.

One can learn everything he needs to know from the pulse, respiration, blood pressure, urine volume, urine sugar, and general condition of the patient. Therefore, I rarely use any blood laboratory work in the treatment of diabetic coma.

The greatest problem which the physician has in the treatment of diabetic coma is his own fear of large doses of insulin. The entire literature of diabetic coma reflects that fear. I remember when we were told to give 20 units of insulin every two hours after an initial dose of 40 or 50 units. Some of us felt that we were very bold when we began to use 100 units as an initial dose and then as much as 40 units every hour. Now, without even measuring the level of the blood sugar we feel that 200 units should be the initial dose and that 50 units should be given every half hour afterward for two to three hours or more in severe cases. Recently a report in the Lancet advises an initial dose of 300 units and I am inclined to follow.

The patient's stomach should be lavaged and the tube left in for constant drainage, for dilatation of the stomach is almost a constant concomitant of this condition.

Infusion of saline (0.9 per cent) is begun at a rapid rate, and when the urine sugar begins to drop rapidly (to a greenish yellow or yellowish green reaction) 5 per cent glucose in saline is substituted. If shock is present, plasma or blood is infused into the other arm. Sodium lactate or even sodium bicarbonate is used in patients who have been in coma for more than two hours. The glucose is continued in sufficient quantity to keep some sugar in the urine so that the large doses of insulin can be continued until the patient is definitely improved. Hypoglycemia during this period must be avoided. The insulin dose and frequency is diminished as the patient improves, unless glycosuria is very heavy at this time.

No elaborate laboratory apparatus or complicated calculation is necessary to the treatment of diabetic coma. Delay in

treating diabetic coma is the greatest cause of mortality of diabetic coma. Yet many a patient's treatment is delayed by precious hours lost in transportation because the practitioner is under the impression that the patient must have the so-called advantages of special laboratory equipment and that one versed in the complexities of the problem of diabetic coma must be on the scene. Actually, everyone can get insulin, everyone can use infusions, and whether the patient be in the small town or the city makes a difference only because there may be more experience with the problem in the city. However, this difference is very small compared to the difference which is made by the loss of time involved in moving the patient. The important thing is that the patient receive large doses of insulin, large volumes of intravenous fluid and salt, and have a gastric lavage immediately, and it makes little difference where he is when this is done. It is a deplorable fact that many diabetics lose their lives because two to four hours are lost in transporting them to a city hospital under these circumstances. This is done because of the impression that many practitioners have that the *treatment* of diabetes mellitus and diabetic coma is a matter of great scientific complexity and that only with the services of ultrascientific methods and ultrascientific specialists can good results be had. It is this fallacious notion regarding diabetes which it has been my purpose to destroy.

DISCUSSION

Dr. Sol B. Stern, Jr. (New Orleans): The treatment of diabetes mellitus centers about two factors—the use of diet and the use of insulin. It has been our experience, and the experience of others, that approximately 35 to 50 per cent of all diabetics can be regulated on diet alone. Of those patients requiring insulin, approximately 70 to 75 per cent require 40 units of insulin or less for adequate control. The latter group can be more or less physiologically controlled by any of the various insulins which we now have at our disposal, i.e., three or four injections of regular insulin or one injection of globin or protamine zinc insulin daily. The severe diabetics, i.e., those requiring over 40 units of insulin daily, deserve special consideration as an extremely large percentage of these cases cannot be satisfactorily controlled by a single daily injection of a depot insulin and may require insulin mixtures.

Are drastic changes in the patient's dietary habits necessary? It is a known fact that the more closely we adhere to a patient's normal living habits, the easier the routine is for the patient and the better his cooperation. It is also a fact that most people eat much the same from day to day unless they are obese. With these thoughts in mind, the eating habits of the nonobese patient were carefully checked and, if diet was adequate, the patient was instructed as follows: (1) omit all sugar, pastry, and soft drinks; (2) eat everything you always have but avoid stuffing; (3) do not eat more than two slices of bread with each meal and, if you have potatoes, eat only one slice of bread; (4) fresh fruit, water-packed fruit, or cheese and crackers may be used for dessert. Our results with this dietary regime have been just as good if not more satisfactory than with the use of carefully calculated diets.

Control vs. Complications: There are two important schools of thought in this connection. The one, headed by Tolstoi, relaxes the standards of control considerably and philosophically tolerates pronounced glycosuria provided the patient is asymptomatic and maintaining his weight. It is Tolstoi's contention that the amount of carbohydrate utilized is vastly more important than the amount of sugar excreted in the urine. The other group attempts to control the patient closely by dietary adjustments, and administration of one or more types of insulin in several injections daily. While it is not universally accepted that lax control of the disease is responsible for the degenerative complications which characterize it, there is suggestive evidence both in animals and man that this may be the case. In the absence of proof to the contrary, it may be hazardous to abandon the goal of normoglycemia in the treatment of diabetic patients.

Hospitalization for regulation of the diabetic patient is usually not necessary since this introduces another variable, i.e., change in activity, into an equation consisting of diet, insulin, and activity thus further complicating treatment.

As regards insulin, protamine zinc insulin is probably the most effective insulin used today. Practically all mild diabetics and a large percentage of severe diabetics can be readily controlled by a single daily injection. We have not found globin insulin to be so effective as protamine zinc insulin and use it mainly to supplement the effect of the latter in a small group of severe diabetics. They are given both insulins in separate injections before breakfast—protamine zinc insulin tends to control endogenous and globin insulin the exogenous carbohydrate metabolism. The use of insulin mixtures and NPH-50 in those cases in which they are indicated has been quite satisfactory.

There are two points which I should like to make

in regard to therapy of diabetic acidosis. First, as Somogyi has pointed out, there are two phases of action of insulin when given in a dosage sufficient to provoke hypoglycemia. At first, liver glycogen increases as glycogenolysis is inhibited and excessive ketogenesis is arrested; later, with hypoglycemia, ketone formation increases as liver glycogen is again depleted by increased glycogenalysis with the "paradoxical" reappearance of ketonuria. Some mobilization of liver glycogen involves the liberation of potassium to plasma, secondary effects of this phenomenon are at once apparent.

The second point is that glucose should be given but only after the blood sugar has begun to drop in order that the glucose diuresis with its obvious consequences will not be perpetuated.

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REFRACTION OF THE DIABETIC PATIENT

P. L. McCREARY, M. D.
LAKE CHARLES

In presenting this paper on refraction of the diabetic patient, nothing new or original is claimed. A brief review of the current literature relative to the transitory visual disturbances associated with diabetes mellitus, and not the more permanent changes found in diabetic cataract, is presented with two case reports illustrating these changes.

We know that changes both sudden and rapid, and gradual or long continued, do take place in the ocular refraction of some patients, and it seems likely that these may occur more frequently than is realized.

Since the original observation by Horner in 1873, it has been known that sudden changes in the refraction occur in diabetes mellitus. The transitory visual disturbances associated with diabetes mellitus occur generally during the acute stage or after an acute exacerbation. It is apparent that observers have noted both myopia, or increase of refraction, and hyperopia, or decrease of refraction, in diabetic cases over a long time. Much speculation was engaged in as to the cause and mechanism of this phenomenon. From studies carried out in 1925, Duke Elder formulated an idea of the direct relationship of these changes to each other and to the diabetes. He states it as a law that: "The refractive power of the eye tends to vary directly as the sugar content of the blood: there is a tendency to hyperopia with decreased sugar and to myopia with increased sugar."

From the Wilmer Ophthalmic Institute, Reese reports agreement of observations there with those of Duke Elder as to relationship of myopic and hyperopic changes in diabetes. He remarks:

"If one makes retinoscopic studies of a diabetic patient, beginning with the patient in a comatose or precomatose state and then through the period of treatment (insulin, diet, salts, fluids) until the patient is finally regulated, it will be found in the beginning there is a state of relative hyperopia, which in turn decreases until the patient's normal refractive state is reached as regulation is finally attained (less insulin and more liberal diet)."

Before insulin treatment the myopic changes were noted more often than the hyperopic. This should be expected, for treatment was less efficient and hyperglycemia was the result so often encountered. However, since 1921 the reverse has been noted. In 1925 Duke Elder's series contained slightly more cases with hyperopic changes, and in 1933 Berke found the hyperopic changes much more frequently.

These refraction changes are of considerable clinical significance. Hemsworth reported that blurring of vision was the first complaint of 34 per cent of patients with diabetes mellitus. In diabetic subjects the near point of vision frequently recedes, owing to a change in the density of the lens. Presbyopia has been noted in the young and is characterized by difficult power of accommodation caused by asthenia resulting from the disease.

The numerous views expressed in different quarters as to the nature of changes involved in the upset of ocular refraction, especially in diabetes mellitus, are of interest. Some of the earlier theories can be briefly dismissed. The old view that accommodative changes are responsible is discounted by the fact that alterations usually occur in older people, that astigmatic changes are often marked, and that atro-

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pine is without effect. The shortening of the axial length of the eye as a result from a loss of intraocular fluid, or that its lengthening results from softening due to edema do not bear examination. The theory as to a change in the refractive index of the ocular fluids due to an increased concentration of sugar, does not seem likely since concentrations far above levels compatible with life would be required to produce an alteration of one diopter. The corneal curvature is found to be unchanged. Therefore, from a process of exclusion, reasoning from the development of astigmatism, and in view of a case of unilateral aphakia reported by Elsching (1923) which showed changes only in the phakic eye, it would seem necessary to postulate that the lens is implicated.

The changes which occur in the lens have not as yet been completely explained, but there are three theories that require mention. In 1925, Duke Elder suggested

"That the myopia associated with a rising sugar concentration was due to hydration of the cortical layers of the lens relative to the nucleus. As the blood sugar rises, provided the available water-reserve is maintained, the osmotic pressure of the aqueous tends to decrease, largely owing to the great elimination of osmotically active substances from the blood in the increased flow of relatively concentrated urine. The lens is a comparatively stable system, not readily participating in the fluctations common to all the body fluids, and therefore it will tend to maintain its original molecular concentration; consequently, in order to establish osmotic equilibrium, fluid tends to flow into it from the chambers of the eye. The lens therefore swells and is deformed, its curvature being increased, further the optical density of its peripheral layers becomes diminished while the nucleus becomes unaltered. On both counts its refractive power is increased, and the eye becomes myopic. If the inflow of fluid is rapid, actual droplets are formed under the capsule of such a size that they can be seen with the slit-lamp, or even with the loupe; eventually a cataract may be formed, sometimes with great rapidity. Conversely, with a fall in sugar concentration, a reverse osmotic flow is inaugurated, and a condition of hyperopia is produced."

The second theory was the hypothesis by Granstrom in 1933 that hydration of the nucleus of the lens was responsible for the hyperopic change. He suggested that in hyperglycemia there was a retention of salt in the tissues which, on decrease of the sugar was followed by hydration. He claimed the lens shared in these changes, the phenomena being more marked in the nucleus since the cortex attained rapid equilibrium with the aqueous. The difficulty about these theories is the impossibility of reproducing the changes in experimental animals by altering the fluid balance of the body either with sugar or salt. Weekers was able to induct myopic changes in animals by the ingestion or injection of galactose, and these were associated with early cataractous changes in the lens. Such changes in these early stages are reversible, and the return of the lens to its normal state is associated with hyperopia. Granstrom in 1937 noted reversible changes in the lens of a precataractous type in some diabetic cases. In 1941 Weekers concluded that the myopia was due to an increased refractive index of the lens due to changes of a precataractous nature caused by a toxic agent; such changes are reversible and on their amelioration hyperopia results. A natural conclusion arising from the systemic effect of the diabetic morbid process is that presence of increased sugar in the refractive media produces the changes.

Regardless of the cause of the changes in ocular refraction, a sudden and seemingly inexplicable myopia should always suggest the possibility of diabetes and direct attention to the urine, and possibly a blood sugar. When occurring in a known diabetic it should suggest a relapse in the progress of the disease. While on the other hand, a sudden hyperopic change points to treatment being too suddenly undertaken or too rigorously applied. The latter condition has become more common since the general introduction of insulin. Regardless of the refractive condition, treatment should be directed to the constitutional disease and not the eye, as the refractive change is transitory, and returns to normal as soon as the metabolic equilibrium can be restored. If lenses are prescribed they should be considered only as an emergency and temporary measure.

CASE REPORT

The following case report is presented:

On September 5, 1947 this patient, a white male, 52 years of age, presented himself for examination, complaining of suddenly noting that while driving he could not see well. He could see better without his glasses. The present prescription had been used for twelve years. General fatigue was the only other complaint. Neutralization of his lenses revealed, a hyperopia of O.D. plus 2.25 sphere with a minus .25 cylinder x 90. O.S. plus 2.50 sphere with a minus .25 cylinder plus 90. The vision with this correction was 20/200 in each eye, and 20/50 and 20/60 respectively without glasses. A manifest refraction revealed a decrease in the hyperopia to O.D. plus 1.25 sphere with a minus .25 cylinder X 90 and O.S. a plus 1.75 sphere with a minus .25 cylinder X 90 and a plus 2.75 sphere O.U. With this correction the vision was 20/20 in each eye. In view of this sudden visual change and our finding of a relative myopia, diabetes was suspected. He was immediately referred to an internist, and a report later the same day revealed a four plus sugar. The blood sugar was 300 mgms. the following day. Under insulin and dietary regime the patient was standardized, and refraction on October 16, 1947, revealed an increase in the hyperopia of O.D. plus 2.75 sphere with a minus .25 cylinder X 90, and O.S. plus 3.00 sphere with a minus .25 cylinder X 90, and a plus 2.75 sphere O.U. for near. The vision was 20/20 in each eye. In discussing this case with the internist it was learned that at a later date this patient developed a high kidney threshold and it was possible for him to have a negative urine, and a blood sugar of 300 mgms. This point is mentioned to illustrate the possibility of not always relying on a urine sugar in cases of diabetes.

The second case illustrates the refractive change taking place in the relapse in the course of the disease in a known diabetic. This patient, a colored male, 70 years of age, presented himself for an eye examination stating that two months ago his eyes had suddenly failed. He had consulted an optometrist who had presecribed the glasses he was now wearing. These were satisfactory at first, but recently he found that he could see better for distance by looking through the reading segment. After further questioning as to his general physical condition, it was learned that he was a known diabetic who had been careless as to his diet, but recently his physician had again regulated his diet and that his urine was now sugar free. It was after standardization of his diabetic condition that he noted his glasses were no longer satisfactory. Neutralization of his glasses revealed a minus .75 sphere O.U. with a plus 2.75 add for near. Manifest refraction at this time revealed O.U. plus 2.25 sphere with a plus 2.75 add for near. The vision was 20/20 O.U.

SUMMARY

In summary, a brief review of the literature as to the causes of refractive changes in diabetes has been presented.

We would like to emphasize that a sudden myopia should always suggest the possibility of diabetes, and direct attention to the urine, and possibly a blood sugar. Occurring in a known diabetic, it should suggest a relapse in the progress of the disease. Regardless of the refractive condition, treatment should be directed to the constitutional disease and not the eye, as the refractive change is transitory.

Two cases have been presented, one with the first symptom of the disease being manifested as a refractive change in the eye, the other a relapse in the course of the disease.

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DISCUSSION

Dr. Penn Crain, Jr. (Shreveport): There are many factors affecting the refraction state of the diabetic. Should we eliminate the very obvious factors such as the retinal changes and the cataracts, we still have a problem which is worth much thought. These conditions along with the occasional nerve paresis, scotomata, and deep corneal changes are just part of the trouble caused by this one condition affecting the eye in just slightly less frequency than lues.

Loss of accommodation, quick refractive changes, and resulting changes in visual acuity we know to be a part of this condition. This rapid loss of accommodation is frequently one of the very first signs of diabetes and is found in some 20 per cent of cases. The exact mechanism is unknown but Rea suggested that glycogen deposits in the ciliary body might interfere with its normal function. Likely the changes in the lens already mentioned play a part. Loss of accommodation in a young person should always suggest the possibility of diabetes.

It has been known for many years that the refractive state of the patient varies with his general condition, there being a tendency toward myopia in hyperglycemia, and hyperopia as the sugar level

of the blood is decreased. These changes vary with the water content of the lens. Reese has shown that changes tend to occur more often in older people but greater changes occur in younger patients.

One point which is seldom discussed is the fact that several weeks may elapse between the time the diabetes is controlled and stabilization of the refractive state of the patient. For this reason changes in lens should be delayed, or if it is absolutely necessary that they be changed, the patient should be warned that further changes may be necessary.

It should be re-emphasized that treatment for these refractive changes for the most part should be directed toward treatment of the general condition.

Dr. Frank W. Pickell (Baton Rouge): A great many diabetics have a very unstable blood sugar, one minute it is high, and ten minutes later it is low, especially in children. What is this effect?

Dr. P. L. McCreary: There are some instances in which individuals may have high blood sugar without any demonstrable changes in the eyes. It affects some and doesn't affect others. If we had the opportunity to follow these changes with the retinoscope, we might be able to see them. It merely aids in the diagnosis of the diabetes. You may find instances where there would be changes and many where there are no changes.

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THE DIFFERENTIAL DIAGNOSIS OF DIABETIC RETINOPATHY

GEORGE M. HAIK, M. D.*
LOUIS A. BREFFEILH, M. D.**
AND
M. R. HARRINGTON, M. D.***
NEW ORLEANS

The medical profession has made wonderful progress in increasing the life span of the individual, but this has also resulted in an increasing incidence of blindness in the aged. The most frequent causes of this condition are glaucoma, cataracts, and retinopathy.

In the State of Louisiana there are 4339 blind persons on record, of whom 1785 are receiving aid to needy blind. There are 66 known diabetics, of whom 38 have retinopathy, 27 have cataracts, and 5 have glaucoma. These figures do not represent the total number of blind persons but only those on file with the central register of the division of the blind in Baton Rouge. There are many diabetics in this group not registered as such.

Recent progress has been made in the use of medications in the treatment of the retinopathies, and the majority of investigators have concluded that the results have been satisfactory but that the drugs are best used in the prevention rather than in the therapy of these conditions. As to the results of these later investigations, there has not been sufficient lapse of time to evaluate their therapeutic value.

The drugs most used have been vitamin P with special reference to rutin, which has an affinity for the control of capillary fragility and permeability, and dicumarol for its effect on the coagulability of the blood. Rutin has been used safely in dosages of from 20 to 120 milligrams daily without any harmful effects, and its combination with vitamin C enhances its therapeutic value. This drug is safe to use on ambulatory patients, while dicumarol is a very dangerous drug which can be used only in hospitalized patients under close laboratory supervision. Before the therapist prescribes this drug, he must be familiar with its use and the dangers of the serious hemorrhages which may result.

We have used these drugs in the treatment of retinopathies with satisfactory results, but we also feel that the greatest therapeutic value is in the early therapy rather than in the far advanced cases of retinopathy.

Unless the correct diagnosis of the disease is made early, the proper therapy cannot be instituted for the prevention of the retinal complications. In diabetes we must not only correct the changes in the blood vessels but the disease itself must be under control and the retina searched for the earliest signs of damage. This is also true

*Professor of Ophthalmology, Louisiana State University School of Medicine, New Orleans, La.
**Assistant Clinical Professor of Ophthalmology, Louisiana State University School of Medicine, New Orleans, La.
***Clinical Instructor, Department of Ophthalmology, Louisiana State University School of Medicine, New Orleans, La.

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in the treatment of renal and hypertensive conditions whereby the primary condition must be controlled if the complications are to be avoided.

Since diabetic retinopathy is one of the most frequent offenders we have chosen this disease for discussion. The occurrence of this condition is increasing, and based upon these figures from the National Health Survey and upon the reports from the insurance companies, we can say that there are approximately 700,000 known cases of diabetes in the United States at the present time. Joslin[1] estimates there are 2,000,000 persons living in the nation today who either have or will develop this disease; while Herbert N. Marks[2] of the Statistical Department of the Metropolitan Life Insurance Company estimates there are 55,000 new cases annually. Thus, approximately 4,125,000 or 2.9 per cent of the population (2.1 per cent of the males and 3.8 per cent of the females) will become diabetic before they die.

Retinopathy is an important complication of diabetes, especially in cases of long duration. The incidence figures of this complication run from 5.1 per cent to 30.6 per cent in diabetics. Wagner[3] noted an increasing incidence of retinopathy when his three series were compared. Retinopathy was present in 8.3 per cent of the 1921 series, in 17.7 per cent of the 1934 series, and in 30.6 per cent of the 1945 series of 1,021 cases. He also found retinopathy in 10.7 per cent of the patients who had had diabetes for less than one year; in 22 per cent of those who had had it for one to ten years; and in 65 per cent of those who had had diabetes from eleven to fifteen years; and in 67 per cent of those who had had it for more than twenty-one years. Dolger[4] found a steady increase in retinopathy especially in the younger age group. This condition was present in 76 per cent of the patients under 30 who had diabetes for more than ten years. He also found the duration of the disease more important than the age of the patient. During a period of twenty-five years not one in 200 patients examined regularly escaped retinal hemorrhages, regardless of the age of onset, the severity of the diabetes, or the type of the treatment. Fifty per cent presented hypertension and albuminuria at the time of the earliest hemorrhage.

In the diagnosis of diabetic changes in the retina, we must agree with Freidenwalder[5] in that there is no typical picture of this condition as seen in other diseases. Yet there are certain changes that occur so frequently in this disease that we must consider them as diagnostic findings. Hemorrhages, exudates, and retinitis proliferans occur so often that Granström[6] classified diabetic retinopathy into four states: Stage 1 could be applied to isolated hemorrhages of the usual small round type; in State 2, these hemorrhages are more severe and in some cases white spots may be present; in Stage 3, there are numerous hemorrhages and white spots of exudates; the final Stage 4 is the grave form with hemorrhage into the vitreous and the resulting proliferating retinitis.

The earliest signs of retinal changes in diabetes are the small, round hemorrhages deep in the retina as were found by Givner and Lodyjensky[7] in their examination of 128 juvenile diabetics, in which pinpoint hemorrhages were present in 3 children, ages 12, 15, and 15, respectively, and all had known diabetes from eight to eleven years. The differential diagnosis in these early stages is not difficult as we can only consider blood dyscrasias and injuries to the eye as the causes of the hemorrhages and the low incidence, history, and blood examination quickly rule out these possibilities.

The hemorrhages in diabetes are venous in origin. The pathology of this venous bleeding is believed due to the slowing of the venous circulation, which results in stasis and nutritional changes in the endothelium of the finest capillaries, and that results in a slow leak of corpuscles into the tissues. The small hole in the vessel wall fails to heal and, instead, the endothelium grows around the mass of extravasated red cells. These masses eventually form a minute sacculated aneurysm connected to the

capillary. This condition was first described by Balantyne and Loewenstein[8] and later elaborated upon by Freidenwalder.[9]

The hemorrhages, being venous in origin, are small, round, and deeply seated in the plexiform layers of the retina. Later, the flame-shaped hemorrhages may be present in the nerve fiber layer and even retinal and vitreous hemorrhages may result. These later complications are not a result of the diabetes, but are the results of the hypertension and, especially, of the arteriosclerosis that occurs in this disease. Any disc changes and edema are also a complication of vascular changes and not of the original disease.

Hypertension of the essential type does not reveal any retinal changes and, as in the malignant type, the hemorrhages along the course of the arteries are a result of the renal and vascular changes. In this condition the hemorrhages are near the disc and flame-shaped. Edema is also one of the prominent signs of this condition. The arteries are small in caliber and reveal arteriospasm, which is believed to be the cause of the hypertension. When a vein crosses an artery there is present a constriction with a dilatation of the peripheral portion of the vein and this is known as arteriovenous nicking.

In albuminuric or renal retinopathy due to nephritis, the hemorhages are similar to those of the hypertensive but the edema is more outstanding, and, since it occurs in those areas where the nerve fiber layer is loosely attached, it is more prevalent at the nerve head and in the macula. The fovea is usually normal but the edema surrounding the macula may appear as though there is a macula hole and the star-shaped figure may be seen as well as striate edema lines toward the disc. At the disc the markings of the margins are obscured. The arteries are spasmodic and small, also, the arteriovenous nicking is prominent. The presence of cotton wool exudates will confirm the diagnosis.

Occasionally obstruction of a small artery, especially in the periphery of the retina, may present a diagnostic problem. The presence of blanching, monocular involvement, hemorrhages, and the obstructed vessel will confirm the diagnosis on close ophthalmoscopic examination.

Exudates in diabetes are small, numerous, appear hardened, and are either white or yellowish white in color. They may be discrete or confluent, forming all types of figures even circinate ones. In albuminuric retinopathy the exudates are dull white or grayish white in color and are known as cotton wool patches. These are superficial and in the area of edema.

Retinitis circinata may be confused with diabetic exudates as both tend to occur in the macular region, but the sudden loss of central vision in one or both eyes would serve to make us suspect a condition other than diabetes. In the latter condition, loss of vision is gradual and only in the late stages. The macula hemorrhages will also aid in the diagnosis of this rare congenital degenerative disease.

Other conditions that may confuse the diagnosis are drusen, which are colloid excrescences on Bruch's membrane, retinitis pigmentosa albiscens, and hereditomacular degenerations. These conditions can be ruled out by histories, ophthalmological, and laboratory examinations.

Vitreous opacities have been mentioned as a differential diagnostic point as the vitreous floaters are not seen in diabetes, but are found in arterial sclerosis, renal and hypertensive retinopathy. If the diabetes is sufficiently far advanced to have large hemorrhages, then floaters may be found.

In conclusion, we may say that the incidence of diabetic retinopathy as well as diabetes itself is increasing. The retinal complication is one of the more serious conditions resulting from the disease in that it affects the activities of these persons. The condition is not related to the age of onset or the severity, but to the length of time that the patient has had diabetes.

The primary retinal pathology is venous and metabolic in origin and characterized by hemorrhages, exudates, arteriosclerosis,

and later retinitis proliferans resulting from large vitreous hemorrhages.

The differential diagnosis concerns itself primarily with vascular diseases, especially those of hypertension, arteriosclerosis, arteriolarsclerosis, and renal conditions.

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DISCUSSION

Dr. Paul J. Azar (Lafayette): The authors of this paper, Dr. Haik and his associates, have chosen as their title *The Differential Diagnosis of Diabetic Retinopathy.* The subject has been covered in a comprehensive manner. Attention is properly called to the increasing occurrence of this complication of diabetes coincident with the gradual lengthening of the life span. The use of the term retinopathy more correctly expresses the true pathological condition, since this essentially is a degenerative process rather than an inflammatory one.

Duke-Elder classifies the retinopathies as follows: arteriosclerotic, renal, malignant hypertensive, the toxemic retinopathy of pregnancy, and diabetic. All of these have in common certain factors: vascular sclerosis, toxemia and, with the exception of some diabetic cases, hypertension. All are characterized by the presence of hemorrhages and exudates. Because of this relation the differential diagnosis is often difficult and sometimes impossible from ophthalmoscopic examination alone. It is possible, and frequently does happen, that more than one of these conditions may coexist.

In diabetic retinopathy the majority of cases show some evidence of arteriosclerosis and sometimes of hypertension, but others with normal vessels and tension have been reported. The hemorrhages are of two types: they may be superficial and flame-shaped, but are usually deep and round and away from the vessels which may show no signs of sclerosis. Hemorrhages may be massive and may occur in diabetics whose condition is fully controlled. The exudates are solid, soapy-looking, with well defined edges, and are distributed irregularly around the macula region. Edema is absent. The prognosis as to life is good, under consistent adherence to the diabetic way of life, but the danger of loss of vision of one or both eyes from massive hemorrhage is ever present.

In arteriosclerotic retinopathy, the retinal vessels show the typical changes. The disc is normal. The exudates are small, well defined and occur in the central portion of the retina. The hemorrhages are usually small and scattered and may or may not occur in relation to the larger vessels. They may be superficial or deep.

Renal and malignant hypertensive retinopathy are particularly important because of their associated grave prognosis. In both conditions the hemorrhages are superficial and may be small or profuse. The exudates are massive and fluffy, the typical "cotton wool." Edema is characteristic of both, but in the malignant hypertensive type papillary and peripapillary edema is extreme, so that the fundus picture is almost indistinguishable from that of brain tumor.

The toxemic retinopathy of pregnancy may occur at any time within the child-bearing period, occurs more frequently in multipara and is always associated with hypertension. The earliest sign is narrowing of the arteriolar lumen, usually due to spasm, and noted first at the nasal periphery. If the toxemia is not controlled, organic changes may take place with the appearance of edema, hemorrhages, and exudates. Massive detachment may occur.

Little can be done in the way of local therapy. The use of dicumarol and rutin, either alone or in combination or the latter combined with vitamin C have not proven satisfactory. It seems that these drugs serve to decrease the increased capillary fragility without altering the course of the diabetic retinopathy. The retinopathies are ocular manifestations of systemic diseases, the management of which belongs in the province of the general physician.

Dr. Paul Marks (Baton Rouge): There is little that can be added to the papers already given. However, I believe that another point of view should be expressed. Considerable doubt has been cast by some people that such a condition as diabetic retinopathy exists as an independent entity. It is quite likely that the true condition is one of arteriosclerotic retinopathy occurring in a diabetic. Thirty per cent of early diabetics have changes in the retina and 100 per cent of them have some change in advanced life. There is no microscopic evidence of any real difference in the blood vessels of a diabetic and a person with

arteriosclerotic retinopathy. Certainly, however, when an ophthalmic patient is seen with a hemorrhage in the retina he should be considered as a whole, and thorough investigative procedures should be carried out until an accurate diagnosis is made.

Dr. George M. Haik (New Orleans): The question raised by Dr. Azar as to the relative value of rutin and of dicumarol has brought us to the conclusion that both of these drugs are of value in diseases of the blood vessels of the retina but their primary value is in their early use. Dicumarol particularly is valuable in cases of early central venous thrombosis. It has not been used a great deal but is now in the investigative phase and holds great promise.

Dr. L. A. Breffeilh (New Orleans): In closing, I would like to thank Dr. Azar and Dr. Marks for discussing our paper.

The question as to the value of rutin in controlling capillary fragility is still unsettled, for over half of the investigators feels that the therapeutic results from the use of this drug have been valuable in the treatment of hemorrhagic retinal diseases. Other investigators are discouraged with their results, but the majority feel that the use of this drug in early cases may be of therapeutic value. The report from the use of dicumarol and the experience we have had with this drug have been excellent and even in hopless cases we have shown visual response beyond expectation. A great deal will be written about the use of this drug in future journals for it has not been used long enough to evaluate the therapeutic results.

The question of retinal changes being diabetic or arteriosclerotic can best be answered by referring to the work of the authorities in this field who have shown histological vascular changes in the diabetic eyes of children and in other eyes of early adulthood. Various surveys of the young age groups have also revealed all the clinical findings of changes of diabetics were vascular and are more related to the duration of the disease rather than to the age of the patient. Should this condition be entirely arteriosclerotic, we do not expect to find evidence of the disease manifested in younger patients but confined more to those of the old age group.

It is only through early examination that we are able to detect these changes and institute treatment primarily for the control of diabetes, and secondarily, for the prevention of vascular changes in the retina. All diabetics, regardless of the severity, age of the patient, or the duration of the disease, should have a complete ophthalmological examination, for the retinal findings will be an indication of the vascular changes which are occurring throughout the body.

THE VALUE OF LUMBAR SYMPATHECTOMY IN ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE

ANALYSIS OF 64 CASES

ROBERT C. LYNCH, M. D.

NEW ORLEANS

For many years arterial peripheral vascular disease has been classified into three main groups: (1) the primarily vasospastic, such as Raynaud's syndrome; (2) that containing a large vasospastic element coupled with obliteration of the arterial lumen, such as Buerger's disease; and (3) that manifested by peripheral vascular insufficiency as the result of severe arteriosclerosis. The last group was formerly considered beyond the aid of surgical measures used to increase the circulation but this opinion is no longer tenable in view of the observations of many investigators as well as our own.

In 1930 White[1] described a technic of blocking the lumbar sympathetic chain with procaine hydrochloride. Subsequently, Flothow,[2] in 1931, and Reichert,[3] in 1933, published observations that chemical interruption of the lumbar sympathetics in patients with severe peripheral vascular insufficiency from arteriosclerosis produced good results which had not been anticipated. Since then, reports have been published on the effect of operative ablation of the lumbar sympathetic chain in arteriosclerotic vascular insufficiency. Ives[4] noted considerable relief in 6 of 7 patients with severe claudication treated in this way. Atlas[5] reported a series of 20 patients treated by lumbar sympathectomy, with one year follow-up in 12; 10 of the latter showed improvement and in the other 2 the coldness and other manifestations in the extremities were relieved. Atlas[6] later increased his original series of 12 patients to 28, all of

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From the Departments of Surgery, Ochsner Clinic and Tulane University of Louisiana, School of Medicine, New Orleans.

whom obtained "uniformly encouraging" results. De Takats and coworkers,[7] who reported the results of lumbar sympathectomy in arteriosclerotic peripheral insufficiency, divided their patients into four groups based upon walking tolerance before the onset of claudication and the severity of trophic changes.

ANALYSIS OF CASES

The records of 64 patients treated at the Ochsner Clinic between 1945 and 1949 by lumbar sympathectomy for peripheral vascular insufficiency as the result of obliterative arteriosclerosis of the peripheral vessels were reviewed in an attempt to evaluate this method of treatment in our hands. All had generalized arteriosclerosis as evidenced by sclerosis of the fundal vessels as well as of other peripheral arteries. In addition, none of these patients had had segmental or migratory phlebitis or arteritis in previous years. In many of them conservative therapy was employed with only moderate to no relief before lumbar sympathectomy was advised. All patients with symptomatic peripheral vascular insufficiency due to arteriosclerosis were considered candidates for lumbar sympathectomy unless a specific contraindication was present. Other conditions confirmed during examination prior to surgical treatment were nerve deafness, saphenous varicosities, hemorrhoids, exogenous obesity, osteoarthritis, benign portal hypertension, essential hypertension, pulmonary emphysema, inguinal hernia, malnutrition, polypoid disease of the colon, bronchiectasis, polycythemia rubra vera, diverticulitis, diverticulosis, cardiospasm, osteomyelitis, renal calculus, and polyp of the vocal cord. Other manifestations of advanced arteriosclerosis were numerous (Table 1). The high incidence of diabetes mellitus is also noteworthy.

The technic employed in this series consisted in exposure of the sympathetic chain through a modified Leriche incision and an extraperitoneal approach. The amount of the lumbar chain excised varied somewhat with the variation in the anatomy but generally included from the second through the fourth ganglia. All specimens were verified by the Pathology Department. The patients were usually ambulatory on the day following operation and were discharged in from seven to ten days. Ordinarily a spinal analgesic was employed, but in some patients with hypertension, or for other reasons, a general anesthetic was utilized.

TABLE 1
RELATED DISEASES IN 64 PATIENTS WITH ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE

Related	Cases
Arteriosclerotic hypertension	22
Arteriosclerotic heart disease	13
Acute thrombosis, peripheral arteriosclerosis	11
Arteriosclerotic gangrene	8
Coronary sclerosis	7
Coronary thrombosis, old	5
Senile arteriosclerosis	3
Optic atrophy, arteriosclerosis	1
Angina pectoris	1
Possibly Related	
Diabetes mellitus	15
Diabetes in neuropathy	1

In contrast to the sex ratio of 4 males to 1 female in a similar group of patients reported by Coller and coworkers,[8] this ratio in the present series was 7 to 1. The youngest patient was 42 years of age, the oldest 78 years and the average 61 years. This corresponds closely with the average age in other reported series.[4, 7, 8] Most patients in the present series were between 50 and 69 years of age.

Bilateral lumbar sympathectomy was done in one stage in 47 cases and in two stages in 5 cases (7.8 per cent). The procedure was performed unilaterally in 12 patients (18.7 per cent), in 8 of whom it was done on the left side and in 4 on the right.

The initial complaints of the patients in this series varied. As seen in Table 2, 54, or 84.4 per cent, complained of pain. Seventeen of these patients had intractable pain of fairly recent onset. The second most frequent primary complaint was intermittent claudication, which occurred in 52

cases, or 81.25 per cent. The duration of this complaint ranged from eight days to ten years with an average of twenty-three months (Table 3). Coldness of the extremity was noted by 27 patients and paresthesia occurred in 23. Most patients complained of numbness and a few noted tingling, burning or tightness of the skin.

TABLE 2

PRESENTING SYMPTOMS IN 64 PATIENTS WITH ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE

Symptom	Cases	%
Pain in extremity	54	84.4
Intractable 17 (26.6%)		
Intermittent claudication	52	81.3
Coldness	27	42.3
Paresthesia/sensory changes	23	35.9
Ulceration	6	9.4
Gangrene	5	7.8

TABLE 3

DURATION OF SYMPTOMS IN PATIENTS WITH ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE

Symptoms	Range	Average Months
Pain in extremity	2 days—10 yr.	26
Intermittent claudication	8 days—10 yr	23
Coldness of extremity	3 wk.—2 yr.	6
Paresthesias	2 wk.—1.5 yr	4
Intractable pain	1 day—6 wk.	3/4
Ulceration	3 wk.—2 yr.	6
Color changes	2 wk.—10 mo.	2

All patients had an abnormally low cutaneous temperature in the lower extremities. This was pronounced in 24 instances, often more on one side than the other. Considerable postural color change with abnormal blanching of the extremity on elevation and varying degrees of sudor or cyanosis on dependency were noted in 45 patients. Delayed filling of the dorsal venous arches of the feet on dependency following elevation was frequently observed. Some atrophy of the involved extremity including atrophic cutaneous changes was recorded in 43 instances. The most peripheral pulse palpable was found to be the distal end of the abdominal aorta in 4 cases (Table 4). As shown in this table, the left extremity was more commonly involved than the right and at a higher level.

TABLE 4

MOST PERIPHERAL PULSE PALPABLE IN PATIENTS WITH ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE

Abdominal Aorta	4 Cases	
	Left Cases	Right Cases
Common iliac	4	0
Femoral	26	18
Popliteal	13	19
Dorsalis pedis	15	18
Posterior tibial	14	14

There was one postoperative death in this series, a case fatality rate of 1.56 per cent. This patient, 66 years of age, had an attack of acute thrombosis of the left femoral artery just above the popliteal. He was known to have arteriosclerosis and hypertension and had survived one episode of coronary thrombosis eighteen months earlier. He expired on the second postoperative day from another attack of coronary thrombosis.

The postoperative complications occurring in the hospital are shown in Table 5. Obviously, in such a group of poor risk patients the incidence of phlebothrombosis and atelectasis might be expected to be higher than in a general survey group.

TABLE 5

POSTOPERATIVE COMPLICATIONS IN 64 PATIENTS WITH ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE

Complications	Cases	%
Phlebothrombosis	4	6.3
Recurrent infection with amputation of	3	4.6
Toe	1	
Lower leg	2	
Pulmonary infarction	1	1.6
Atelectasis	3	4.6
Neuritis	2	3.1
Gastric dilatation	1	1.6
Coronary thrombosis	1	1.6

Amputation was performed on 5 patients although 11 patients were seen with preoperative ulceration or frank gangrene. In one instance because of osteomyelitis of the second phalanx, the toe was amputated at the same time that lumbar sympathectomy was done; healing was by primary intention. The left great toe was amputated eighteen days after sympathectomy in an-

other patient because of recurrent infection. In a third instance the right thigh was amputated two days after sympathectomy because of gangrene of the foot and toes. In the fourth case amputation below the knee was performed on a second admission to the hospital one month after sympathectomy for relief of intractable pain. In the fifth case amputation below the knee for intractable pain was carried out two months after sympathectomy. Examination of the specimen revealed complete arteriosclerotic obliteration of the lumen of the anterior and posterior tibial arteries.

Fifty-two, or 81.25 per cent, of these patients have been followed for periods ranging from three months to four years (Table 6). The results of subsequent examinations were classified under three main groups. The "excellent to good" group included those patients who were either asymptomatic or felt only slight fatigue in the foot or leg after more than average periods of walking or standing, but in whom the feet remained warm, dry, and of good color. The result was considered fair if the patient remained comfortable but normal activity was restricted if either abnormal postural color change remained or complaints of uncomfortable coldness of the extremity persisted. Under poor results have been included those patients who continued to have intractable pain or only slight alleviation of symptoms.

TABLE 6

RESULTS OF LUMBAR SYMPATHECTOMY IN 52 PATIENTS WITH ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE

Follow-up	Excellent to Good	Fair	Poor	Total
1 to 4 yrs.	19	6	1	26
6 months to 1 year	11	4	1	16
3 to 6 mo.	6	2	2	10
Total	36 (69.2%)	12 (23.07%)	4 (7.69%)	52

Of 26 patients examined more than one year following lumbar sympathectomy, 19 had an excellent or good result (Table 6). In 1 of these patients Parkinson's syndrome developed fifteen months postoperatively. Six patients were improved; in 1 of these considerable improvement was noted for eleven months, but then "tightness" of the thigh muscles developed after exercise. This patient expired two years postoperatively from an attack of coronary thrombosis. Another patient has a limited exercise tolerance because of anginal pain, but has noticed weakness of the calf muscles with continued slow walking. One patient experienced continuation of intractable pain postoperatively necessitating amputation at the lower thigh level.

Of the 16 patients examined between six months and one year following operation an excellent or good result was obtained in 11 and a fair result in 4. Two patients in the latter group expired ten and eleven months postoperatively from cerebral hemorrhages. Both had experienced no difficulty in walking and no further pain in the leg after the operation. One patient in this group was well for ten months postoperatively. Following the use of a new pair of shoes this patient noted pronounced color change in the second and third toes of the left foot. He was readmitted to the hospital with dry gangrene of the tips of these toes, which responded to conservative therapy. The one patient in whom a poor result was obtained was admitted with senile arteriosclerosis as well as impending gangrene of both feet, the left worse than the right. On examination ten months postoperatively the feet were dry and warm, although greater postural color change than normal was noted. At this time the patient complained chiefly of aching pain in the legs on exercise or rest, transitory in nature and usually allayed by acetylsalicylic acid.

Of the 10 patients examined between three and six months postoperatively, an excellent or good result was obtained in 6. One of the 2 patients with a poor result complained of stiffness but no pain in the calf muscles on walking one and a half blocks. This patient had made no effort to follow the measures outlined for control of his severe diabetes mellitus. The other patient with a poor result still had aching pain in both legs following mild exertion. This patient had been admitted primarily

with severe, incapacitating pain and impending gangrene of both feet.

As shown in Table 6, in the series of 52 patients, 36, or 69.2 per cent, obtained an excellent or good result, 12, or 23.07 per cent, a fair result and 4, or 7.69 per cent, a poor result. Since this series comprised patients with far advanced arteriosclerotic disease, all 64 patients were not expected to benefit greatly from lumbar sympathectomy and in many of them the operation was advised in order to obtain a better stump ultimately.

DISCUSSION

Several authors[4, 9, 10] have called attention to the significance of vasospasm in patients suffering from arteriosclerotic occlusive peripheral vascular disease. This may be demonstrated readily by procaine block of the lumbar sympathetic chain. However, it has become increasingly apparent that the subjective and objective relief of vasospasm which follows this procedure is not a true criterion of the expected result in cases of arteriosclerotic obliteration. Beneficial results after lumbar sympathectomy occur in many patients in whom little or no response followed careful performance of procaine lumbar block.

After the independent demonstration of the neuromyoarterial glomus or arteriovenous shunts in the distal part of the extremities by Sucquet[12] and Hoyer,[13] Grant[14] established the fact that these were under vasomotor control. Using a preparation of the rabbit's ear, he demonstrated that sympathetic stimulation caused these shunts to close. Clark[15] was able to show that following injury of a sympathetic nerve there is constant dilatation of these shunts for ten to fourteen days and that thereafter the smooth muscle acquires tonicity with narrowing of the lumen. Other experimental work indicates that blood flow through peripheral muscle is not influenced by abolition of the lumbar sympathetic chain. Grimson and Shen,[16] working with skinned legs, found the opposite to be true. The oscillometric studies of Atlas[5, 6] revealed an increase in the vascular bed over a period of twelve to twenty-five months in cases of peripheral arteriosclerosis following lumbar sympathectomy. Freeman and Montgomery,[11] who used an electrical claudication test to determine accurately the results in such cases, reported a definite increase in work ability in 7 of 12 patients with subjective improvement in 3 more.

This gradual increase in the capillary bed following lumbar sympathectomy may account for the increasingly good results in the patients followed for the longest period in our series. DeTakats and coworkers[7] demonstrated a loss of myelin of somatic nerves in extremities with greatly decreased blood supply leading to intractable pain. This is more noticeable in patients with diabetes mellitus. The irreparable loss of myelin may account for the poor subjective results in patients with severe prolonged pain preoperatively. In the present series 4 of the patients requiring amputation had diabetes mellitus.

There were no cases of "paradoxical" gangrene in this series. Atlas[5, 6] reported 3, and Coller and associates[8] 2 cases in which lumbar sympathectomy was followed by diffuse patchy areas of gangrene with normal intervening tissue. The process was slow and progressive ultimately necessitating amputation. It has been suggested that the arteriovenous shunts of Sucquet[12] and Hoyer[13] are responsible for this phenomenon, the blood flowing through them at the expense of the nutrient capillary circulation during the immediate postoperative period.

SUMMARY

Follow-up studies ranging from periods of three months to four years were conducted in 52 of 64 patients treated at the Ochsner Clinic by lumbar sympathectomy for arteriosclerotic peripheral vascular disease between 1945 and 1949. Of these 69.2 per cent obtained excellent or good results and 23.07 per cent fair results. Only 4 patients, or 7.69 per cent, received little or no benefit from the operation. Although there were no deleterious results in this series, this possibility is discussed.

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DISCUSSION

Dr. Mims Gage (New Orleans): I enjoyed Dr. Lynch's presentation very much. I only wish to comment on the preoperative block of the lumbar sympathetics as an aid to radical surgical procedures. Two types of peripheral disease are encountered clinically regardless of the etiology: those in which the spastic element of the vascular components overshadows the organic obliteration and those in which the organic pathologic process predominates. It is the first type that is remediable by lumbar sympathetic ganglionectomy.

It is to distinguish between these two types that lumbar block of the sympathetics with procaine hydrochloride is justifiable. Many times lumbar block is disappointing, i. e., there is no response to the block. This in the main is due to failure to flood the retroperitoneal cellular tissue that surrounds the sympathetic chain with the procaine. Therefore, I believe that all patients with peripheral vascular disease who have a clinical deficiency of the arterial supply should have a lumbar sympathetic ganglionectomy. Removal of the second and third ganglions is considered all that is necessary to denervate the lower extremity. The distribution of the ganglionated chain is so variable that I always take out the lowest ganglion and then the upper two (3 and 2) or the trunk even though the block did not produce a favorable response. As a result of my experience I have dispensed with the preoperative block in the majority of cases.

As Dr. Lynch has told you we have been able to amputate at a lower level in some patients with arteriosclerotic gangrene by performing lumbar sympathectomy on the involved side first. In certain patients with diabetic gangrene admitted to our service at Charity Hospital, we have saved an extremity by treating the infection with incision and drainage, antibiotics, and lumbar sympathectomy. Therefore, I would advise that lumbar sympathectomy be done early in all cases of organospastic and spasto-organic arterial deficiency of the lower extremities and cervicodorsal sympathectomy for the upper extremities.

Dr. Lynch (In conclusion): I should like to thank Dr. Gage for his able discussion. I would also like to point out that DeTakats and Coller use block primarily in defining a group of patients in whom they feel paradoxical gangrene is an impending affair. On patients with intractable pain or severe atrophic changes they feel that if the symptoms increase following lumbar sympathetic block, sympathectomy is contraindicated. They feel, however, even though they come to amputation, that amputation may be carried out successfully at a lower level without performance of lumbar sympathectomy.

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FACTORS INFLUENCING THE CHOICE OF ANTIBIOTICS IN THERAPY*

ALFRED B. LONGACRE, M. D.†

NEW ORLEANS

Since the discovery of the clinical application of the sulfonamides to the treatment of infectious diseases, continued advancement in the physiological control of infections has been made by the discovery of the antibiotics. The mode of action and the selectivity of the various antibiotics have permitted a relatively safe attack upon the etiologic organisms. The antibacterial

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†Department Surgery, Louisiana State University Medical School.

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spectrum of the antibiotics has been greatly extended by the recent discoveries of aureomycin, chloramphenicol, and bacitracin. As new antibiotics are made available the scope of this spectrum should be further increased. Inasmuch as the antibacterial range for each of the antibiotics overlaps that for the other antibiotics, and inasmuch as each of them has a limited spectrum in which it is apparently the only specific antibiotic, their therapeutic success will depend upon an intelligent appraisal of the many factors influencing their clinical and antibacterial action.

It is a recognized fact that it is highly desirable to commence specific antibacterial therapy in the treatment of infections with a minimum of delay. The choice of the antibiotic to be used as the initial treatment need not be delayed pending an analysis of the bacterial flora and the determination of the antibiotic sensitivity of the organisms isolated. Inasmuch as such studies are time consuming, they only permit continuation of the infection if therapy is delayed pending their completion. An antibiotic should be administered as soon as is practicable after the patient comes under the care of his physician. A careful clinical appraisal of the location, mode of onset, duration of the process, and other familiar clinical features will often permit a possible etiologic diagnosis of the bacteria involved. If the clinical evaluation of a case supports the diagnosis of an infection caused by bacteria most likely to be sensitive to any one of the antibiotics, then it follows that that is the antibiotic of choice for the initial therapy. In some instances much helpful information can be obtained from a gram stain of the material obtained from the infection. The continuation of the antibiotic selected or the rational change to a more effective antibiotic can then be determined by adequate laboratory procedures. In the cases of mixed infections it may be necessary to employ more than one antibiotic.

Rational antibiotic therapy requires not only a careful clinical evaluation, but is probably more dependent upon a knowledge of bacterial sensitivity of the flora in the infection under immediate consideration. With few exceptions all pathogenic microorganisms are capable of establishing an infection in any of the tissues of the body. It therefore becomes self evident that the anatomical location, though indicative of the most likely species to be recovered in bacteriologic studies, is far from being diagnostic and may often be misleading. (As mentioned, these anatomic features may prove to be a guide for the initial choice of an antibiotic.) Also the anatomical location of the infection will in certain instances determine the route of administration of an antibiotic in order to be sure that the antibiotic becomes most accessible to the infection. Penicillin, for example, must be given intrathecally to obtain adequate therapeutic levels in the spinal fluid. In other locations it will be advisable to apply the antibiotic locally in order to secure maximum concentrations at the site of the infection. This is particularly advantageous in certain infections of the serous cavities and in superficial abscesses and ulcerating lesions, as well as in open wounds. Likewise, in cases of typhoid fever, bacillary dysenteries, amebiasis, and other enteric infections, best results are obtained when combined oral and parenteral administration is employed.

The continuation of the successful antibiotic treatment of an infection is dependent upon information obtained from adequate bacteriologic analysis of the bacterial flora in any specific case. The intelligent application of this information, coupled with adequate supportive therapy is the only basis for rational antibiotic therapy. That this approach to the problem is the only tenable one is repeatedly being attested to by those not too infrequent cases in which the successful outcome is either being delayed or denied for want of this information. In addition to the bacterial analysis, which does identify the etiologic species of the flora in an infection, it is in many instances necessary to determine the antibiotic characteristics of the particular strain or strains involved in any given case.

Until such information is available the rational therapeutic approach will be incomplete, if not impossible.

Unfortunately, the antibacterial range of all antibiotics does not include all species of pathogenic organisms, and likewise the spectrum of a single antibiotic is not sufficiently broad to include all species of the present antibiotic sensitive organisms. Consequently, it is essential to know the range of each of the antibiotics. It so happens that the bacterial spectrum of each antibiotic can be divided into at least two main phases. The first of these phases includes those species of microorganisms against which the respective antibiotic is most specific and in many instances is the only antibiotic effective against these strains. Even though the bacterial range of inhibition by penicillin includes many species of pathogenic microorganisms, penicillin is considered most effective against the gram positive cocci and to be practically inactive against the various strains of the gram negative bacilli. Streptomycin, on the other hand, has marked antibiotic effect against many strains of gram negative bacilli, but has only a weak antibiotic action against the gram positive cocci. Bacitracin has a spectrum similar to that of penicillin. However, it complements penicillin in that it is effective against many of the strains of gram positive cocci, which are penicillin resistant. In work in our laboratory and in reports published by Meleney and others it has been shown that bacitracin probably has a much wider spectrum of antibiotic activities against gram positive cocci than does penicillin. However, this advantage is offset by the apparent lower nephron syndrome which develops in approximately 16 per cent of the cases. So far this lower nephron syndrome has been apparently more alarming than is indicated by the results obtained. It is hoped that this untoward manifestation resulting from bacitracin therapy will be obviated upon further purification of bacitracin. This untoward manifestation is only seen in parenteral administration of bacitracin, and does not develop following its local application or oral administration. Chloromycetin and aureomycin have bacterial spectra which are very similar to each other but differ from the other three antibiotics previously mentioned. Their action against the rickettsial diseases and other enteric diseases, including the typhoid and dysentery group, and also certain of the virus infections, is not possessed by the other antibiotics.

However, in addition to being familiar with the gross species classification of antibiotic activity of each antibiotic it is necessary and important to realize that strains within these species vary in sensitivity to the various antibiotics. The range of this variation runs from the very sensitive strains to those which are completely resistant. Whereas, when penicillin was at first thought to exert antibiotic inhibitions against approximately 90 to 98 per cent of staphylococci, it is now known that only approximately 65 to 70 per cent of pathogenic staphylococci are sensitive to penicillin. Withot being specific, such variations can be shown to exist for other antibiotics against the different strains of other microorganisms. It is not permissible to assume that a bacteriologic species identification of the flora of an infection is always completely sufficient as a guide in rational antibiotic therapy. The knowledge can be of great assistance in determining the most likely antibiotic to be effective and in many instances this may be the only information necessary. However, because of the variation in the sensitivity in the various strains, it is almost mandatory that strain sensitivity be determined for a continued period for a rational antibiotic therapy.

At present the methods of determining strain sensitivity of various organisms require time and trained technical assistants, as well as a fully equipped laboratory. The most accurate method for determining the degree of sensitivity of any strain is by titration of an antibiotic against that strain. The various plate methods now being used are at best only suggestive and cannot be relied upon as a final criterion. In the laboratory of the Louisiana State University School of Medicine a plate tech-

nic which is simple and can be carried out in any small laboratory is being developed. As promising as this technic appears to be, considerable more work, including checking of the plate reading against actual titration, will have to be carried out before it is released for general use. The development of such a technic would be invaluable and make the choice of the antibiotic in any infection a relatively simple procedure.

In addition to the strain sensitivity to an antibiotic, there are many other features of antibiotic actions which enter into the success or failure of this form of treatment in any given case. It has long been known that the individual strains of certain streptomycin sensitive species may become either streptomycin resistant or were at the outset streptomycin fast. Inasmuch as the various species of bacteria recovered from an infection are not strain pure, it is conceivable that the species recovered should be composed of antibiotic sensitive, antibiotic resistant, and strains which develop antibiotic fastness. Consequently, in these infections in which these antibiotic properties may be possessed by the various strains in the flora an early good response to streptomycin therapy might be no indication of the ultimate success or failure in any given case. In addition to certain strains demonstrating antibiotic fastness and resistance, there are other less frequent strains which by in vitro tests are apparently streptomycin dependent. This streptomycin dependency is not very common, but if it so happens that the pathogenic strain involved possesses this quality, the course of the infection could easily be aggravated and accelerated. It is not known whether or not strains sensitive to the other antibiotics are dependent or antibiotic fast, and consequently, at least for the present, these properties are peculiar to streptomycin.

However, in a similar manner from a clinical point of view, the antibiotic activity of penicillin against a penicillin sensitive strain of bacteria can be negated by the development of penicillinase in the infection. This appears most frequently in wounds of a mixed flora containing one of the gram negative bacillus group of enteric origin. The exact nature of penicillinase is not fully understood, but both in vivo and in vitro it has been demonstrated that penicillinase can completely inhibit the action of penicillin. It, therefore, stands to reason that in infections possessing a mixed flora in which one of the species recovered is penicillin sensitive, and one of the other species recovered is a penicillinase producing gram negative bacillus, the action of penicillin can be completely obviated by the development of penicillinase in the infection. This does not necessarily hold for all types of infections, but should be constantly kept in mind in treating an infection in which the possibility of the development of penicillinase exists. In such infections, should the clinical course be unsatisfactory, one of two courses of treatment is possible. Therapy should be directed at either eliminating the bacteria which produce penicillinase or should be changed to an antibiotic which will inhibit the organism and the action of which is not modified by any of the products present or which may develop in the infection. This information should be obtained early in the course of the infection, for in many instances persistent use of an ineffective antibiotic might be disastrous.

Bacterial synergism is the development of an infection dependent upon the combined action of two or more bacteria and not on any individual species of bacteria. Probably the outstanding clinical illustration of this is synergistic skin gangrene which was first described by Meleney. In this infection two organisms are responsible, namely: a microaerophilic streptococcus and a coagulus positive staphylococcus. Recent investigations, which have not yet been published, indicate that synergistic action of bacteria may be more common than has previously been realized. The significance of the synergistic action in antibiotic therapy needs further clarification. However, in cases in which true bacterial synergism is necessary for the development of an infection, it is conceivable that an antibiotic directed at any one of

the synergistic dependent organisms with its resultant elimination from the infection, might possibly be sufficient in itself to control that infection, in that once a synergistic relationship is destroyed, the original infection is no longer possible. However, if the remaining organisms in such a lesion possess pathogenic properties, they might be capable of producing an entirely different infection. Consequently, in such an infection it would probably be better to use one or more antibiotics, so that the combined therapy would include the entire bacterial spectrum of the infection.

More recent studies of antibiotics are demonstrating that under certain conditions the principle of antibiotic synergisms might possess a therapeutic advantage. Antibiotic synergism can be defined as the increased inhibition resulting from the combined action of two or more antibiotics acting together. This increased range will vary tremendously under different conditions, but is of such magnitude that a simple summation of the expected action by the responsible antibiotics will not explain it. This synergistic relationship of antibiotics was first demonstrated by Eagle in his studies of syphillis in rabbits. He used both bacitracin and penicillin for these experiments and demonstrated that even though penicillin was far superior to bacitracin in controlling syphillis in rabbits, when both antibiotics were used together the individual dose of either antibiotic and of both antibiotics could be reduced to a very small fraction of that necessary to control the disease when either of them was used separately. In a recent case of subacute bacterial endocarditis from which a strain of alpha hemolytic streptococcus was recovered, laboratory tests showed that streptomycin and aureomycin definitely inhibited growth of this organism. However, when either or both antibiotics were used in this case, the clinical course was not modified and the blood culture remained positive. In vitro investigation demonstrated that when a small part of penicillin was added to the aureomycin in the test solution, the bacterial inhibition was greatly increased. In this particular instance this happened in spite of the fact that the streptococcus under investigation was resistant to concentrations of penicillin considerably larger than that added to the aureomycin in the test carried out above. As a result of these tests penicillin was added to the therapy in this case, and within a period of four days of combined therapy the blood culture failed to grow out the streptococcus, and to the present time this patient remains a clinical cure. That similar synergism exists between other antibiotics in other infections and against other strains of bacteria needs considerably more investigation. Incomplete studies in the antibiotic laboratory at L. S. U. School of Medicine have demonstrated antibiotic synergism against many species and strains of laboratory organisms. The clinical application of this principle should be constantly kept in mind in cases which fail to respond as expected to antibiotic therapy.

When penicillin was first used clinically, the quantities available were insufficient to permit indiscriminate and unlimited use. The dose employed was considerably less than that which is commonly used at the present, yet the results were sufficiently gratifying to warant the government to subsidize the erection of large plants so as to increase the production to meet the demands made on it by the war. It was not until after the war that penicillin became available in sufficient quantities to reduce the price so as to permit its widespread use prophylactically and therapeutically in doses far in excess of those previously used. In discussing dosages of any of the antibiotics, the above references to the use of penicillin will apply in a general sense.

The general feeling is that it is better to use too much antibiotics than to use an insufficient amount. There is no question that this is a good rule to follow but it should also have limitations to avoid unnecessary waste. The only important general consideration is to be sure that the antibiotic is present at the site of the infection in sufficient concentrations to exert the maximum effect. At present there are

no methods available which are practical to determine the dose of an antibiotic in any given case. This is particularly true when one considers the various routes of administration, the various preparations of the antibiotics, which include various modifications, so as to delay or increase its rate of absorption; the various concentrations available to various tissues, cavities, fluids, and the rate of excretion in relation to the rate of absorption.

When penicillin was first introduced, the parenteral administration of an aqueous solution of various concentrations was the only approved method for the administration of penicillin. Because of the rapid rate of its disappearance, it was necessary to repeat the dose every four hours. The introduction of modified forms of penicillin, including those suspended in various vegetable oils, beeswax, procaine modifications of penicillin, and the procaine modifications mixed with monosterate, have all not only decreased the rate of absorption, but have been proven to maintain adequate blood levels for varying lengths of time. In general, the fortified procaine penicillin suspended in distilled water is probably the most practical. Most of these products available are capable of maintaining an adequate therapeutic blood level for the more common cases for a period of eighteen to twenty-four hours, following the injection of a single dose of 400,000 units. In some instances the blood level will persist for a longer period of time but in that this is inconstant, it is not rational to rely on the single dose lasting for more than twenty-four hours. In almost all instances, excepting those infections in which the etiologic organism is only susceptible in relatively high concentration of penicillin, will this method of administration prove unsatisfactory. Recent investigation has also shown that the newer forms of oral penicillin are capable of attaining and maintaining an equally effective therapeutic blood level for from four to six hours. The dose of the oral tablet should not be less than 200,000 units every four hours. These tablets need further clinical trial, but if the clinical results compare with those of the other routes of administration, and there is every indication that they should, it is conceivable that in the future this will be the route of administration in most instances.

The dosages of the other antibiotics have been fairly well established and, with the exception of bacitracin, should be fairly well understood. Bacitracin has only very recently been released by the Food and Drugs Administration for parenteral use, and then only under very restricted conditions. This has been brought about by the fact that in certain instances the administration of bacitracin produces a definite lower nephro-syndrome of varying sensitivity. Inasmuch as this has never been shown to be irreversible, and in that in certain specific instances bacitracin is the antibiotic of choice, it has been necessary to make it available under these conditions. For the present the dose should not exceed 10,000 units in a 2 per cent procaine solution every eight hours. All patients receiving bacitracin should have suitable studies to check the signs of kidney irritation. If this routine is followed, the continued administration will have to depend upon laboratory clinical evidence of the degree of kidney reaction.

Comment should be made as to the oral dose, for it is known that almost all of these antibiotics exert their action on bacteria and some protozoa and ameba in the intestinal tract. Of the antibiotics used, bacitracin and aureomycin are probably the most effective in cases of intestinal amebiasis. In those diseases of infection caused by the salmonella, chloromycetin and aureomycin are at present the antibiotics of choice. The local application of antibiotics directly to infections has proven to be very advantageous. This can be accomplished in various forms such as ointment, liquid suspension, compresses, and as the aerosols. The advantage of local application is probably limited to the surface bacteria against which it can be applied in much higher concentration than when either parenterally or orally administered. There is very little in-

formation available as to the bacterial spectrum of any of the antibiotics when tested in concentration comparable with those used in local application. Recently we have had occasion to investigate this because of an infection in which the clinical response was very dramatic, but which according to our laboratory sensitivity test, should not have been so. The test was then set up in which the test dose was equal to the concentration of the bacitracin used in the solution which was applied locally to the wound. In these concentrations bacitracin completely inhibited even the gram negative flora which previously have been shown to be completely resistant to bacitracin. Consequently, it is important to make sensitivity tests of the bacteria at the concentrations expected, depending on the route of administration if an accurate evaluation of the antibiotic activity is to be expected.

In this discussion of a few of the factors concerned with the rational approach to the use of antibiotics in infectious diseases, it becomes apparent that as yet there is no single antibiotic with a wide enough spectrum of antibacterial activity to permit its continued use in a prolonged infection without adequate bacteriological determinations to support such therapy. It has been mentioned that shotgun therapy, consisting of a mixture of all the existing antibiotics, might eliminate the studies necessary to determine the antibiotic of choice. Regardless of whether or not such a procedure would be effective, it is not to be considered a safe, rational, or approved form of therapy. It should not be necessary to advance the arguments condemning such a procedure, as upon a little reflection it immediately becomes self evident. There is no question that relief from suffering, the decreased fear of infection, the decreased morbidity from such infections, the lessening of crippling from specific infectious diseases, and the saving of life from previously thought hopeless infections has followed the therapeutic application of antibiotics. It is not the purpose of this discussion to in any way detract from these accomplishments; to categorically classify the efficacy of all the antibiotics; nor is it the purpose of this paper to establish rigid rules governing the administration of antibiotics in infectious diseases. It is impossible to establish such rules, for the inherent properties of the antibiotic in relation to the various bacteria as reflected in the clinical results have previously been determined on the laws of nature which cannot be governed. Many of the facts mentioned in this discussion are probably well known, but it is the failure to apply these principles which places antibiotic therapy on a trial and error basis. The facts enumerated represent an attempt by investigators to discover these laws, so that their application in the treatment of infectious diseases might possibly be more specific, and therefore, placed on a more rational basis. The details of the investigations pertaining to all of the points have been confirmed by numerous investigators and can be found in the recent literature.

It is realized that adequate facilities for these determinations exist only in the medical centers and the hospitals of the larger communities. However, the various centers concerned with the rational antibiotic therapy and their dependency upon adequate laboratory facilities, only serve to emphasize the increasing importance of having all forms of laboratory facilities available for the practice of modern medicine. These laboratories cannot be discriminately limited to any one field, for the recent advances in all fields of modern medicine are bringing the patient and the laboratory closer together. Such facilities need not be elaborate and can be established in strategic points so as to be available to almost every community. It is the problem of each community to provide such facilities, for they are an integral part in contributing to the happiness and health of the community.

SUMMARY

It has been pointed out that a rational approach to antibiotic therapy is necessary for the intelligent application of antibiotics in infectious diseases. Of utmost importance is an accurate clinical evaluation which leads to a more accurate choice of

the antibiotic for initial therapy. Antibiotic therapy may vary somewhat with anatomical location, but is entirely dependent upon the correct antibiotic reaching the sensitive organism. In addition to making this antibiotic available to the bacteria, it is necessary that the concentration of the antibiotic at the desired seat of activity be of sufficient strength to perform its function. Even though antibiotics are in a very gross way species specific, the strain variation of the relationship between antibiotic and organism is of such magnitude that the species relationship is only grossly reliable in determining the antibiotic of choice. The importance of strain specificity as related to antibiotic sensitivity cannot be overemphasized. Some of the individual properties of the different antibiotics including resistance, antibiotic fastness, and dependency have been mentioned. The possible relationship of bacterial and antibiotic synergism has been discussed. The route of administration and dosage is dependent upon many factors, and cannot be categorically determined for any group of infections, but must be determined for each individual and specific case. There is little question that, if the application of antibiotic therapy is put upon a more rational basis, the ever decreasing number of tragedies from infectious diseases will continue to decrease.

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CURRENT MANAGEMENT OF ACTINOMYCOSIS

R. GORDON HOLCOMBE, M. D.
ROBERT O. EMMETT, M. D.
LAKE CHARLES

Actinomycosis is not a common condition. However, like many other infections producing granulomatous reactions, it is resistant to treatment and pursues a notably chronic course, thereby justifying a periodic briefing as to the most acceptable therapy currently employed. The management of these cases has been considerably improved in recent years by the development of less toxic, more effective antibiotics, and by an improved understanding of ways and means of increasing the patient's resistance to the disease and tolerance to extensive surgical procedures. Ineffectual attempts at destroying the causative actinomycete by specific drug therapy alone as a means of curing the disease have been replaced by a more realistic approach toward arresting the condition by the use of proper surgical procedures in conjunction with more adequate antibacterial therapy and more comprehensive physiologic support of the chronically ill patient.

Presented at the Seventieth Annual Meeting of the Louisiana State Medical Society, in Baton Rouge, April 25, 1950.

ETIOLOGY

Any discussion of treatment requires a word or two relative to the causative organism of this disease. It is of more than passing importance that the fungi formerly grouped together as actinomycetes capable of producling actinomycosis, are now recognized by those best informed on the subject as belonging to two main groups: the Nocardia, which are aerobic organisms, and the Wolff-Israel actinomyces, which are anaerobic or microaerophilic. The Nocardia, or aerobic actinomyces are responsible for very few actinomycotic infections in man. The Wolff-Israel actinomycete, which is an anaerobe, is responsible for the vast majority of human as well as bovine infections.

Although details concerning the portals of entry of the ray fungus into the body tissues are lacking, two concepts are current; that of Bostroem, which contends that human actinomycosis is associated with bovine actinomycosis directly or indirectly, and that of Wolff-Israel, which considers the disease endogenous and unassociated with environment. Insofar as the majority of infections are produced by anaerobic or microaerophilic actinomyces, the Wolff-Israel concept is to be preferred. Considerable emphasis must be attached to the anaerobic and parasitic nature of pathogenic actinomyces. Wangensteen[1] believes that the presence of oxygen-consuming secondary invaders fosters a pleasant anaerobiasis and that a full appreciation of this belief should influence the rationale of therapy. The role of macrophages in the spread

of fungus filaments by continuity and the tendency of the infection not to spread across endothelial or epithelial barriers are well established characteristics of the disease.

GROSS AND MICROSCOPIC FINDINGS

Salient gross features include a central area of abscess formation surrounded by highly vascular indurated zones, the latter being connective tissue proliferation, an attempt on the part of the body to incarcerate and limit the spread of the causative organisms. Fistulization and discharge of yellowish seropurulent exudate containing sulphur granules occurs with rupture or drainage of the centralized abscess. The histopathology of actinomycosis in the human reveals a chronic, suppurative, inflammatory condition which is nonspecific except for the presence of actinomyces situated centrally either as scattered mycelia or compact as granules. This fact is of importance in diagnosing the condition by biopsy, as should the mycelia not appear in biopsied material a positive pathologic diagnosis cannot be made, a fact contributing in certain instances to late recognition. The immunity of the lymphatics as a root of local spread and the uncommon blood stream metastasis are characteristics not ordinarily found in other infectious granulomas.

THERAPY

The most notable therapies of the past have included such drugs as iodides and thymol, and also x-ray therapy. The literature on the subject of actinomycosis is filled with claims of successes and failures in the management of the disease by one or more of these measures with or without surgery as an adjunct. The high incidence of recurrence, the inaccurate identification of the organism involved, the lack of uniformity in grouping cases according to extent of involvement for statistical reviews, and the unrestrained enthusiasm for new therapies, have all contributed to a confused literature. The splendid articles by Wangensteen,[1] Kolouch and Peltier,[2] Gage, Lyons and DeCamp,[3] as well as the monograph by Zachary Cope,[4] have helped to clarify and organize a rational approach to this disease. It is apparent that the iodides are ineffectual in the management of actinomycosis and, as stated by Kolouch,[2] "The universal application of potassium iodide to human actinomycosis is an example of a world-wide medical hebetude resulting from Thomason's ignorance of the bacteriology of the disease to be treated." Thomason had originally recommended the use of iodide therapy on a basis of its effect on what he thought was a case of lingual actinomycosis, but what is now believed to have been a case of actinobacillosis, a condition which affects the bovine tongue and which responds dramatically to potassium iodide therapy. Even today iodides are being used in the management of the disease and it is considered of importance to raise a question as to the actual danger for which iodides may be responsible in the management of actinomycosis. On theoretical grounds at least, potassium iodide may be considered capable of weakening the body's line of defense against the organism. In this regard we recall an article by Landis[5] which appeared in 1913, in which he boldly challenged the use of iodides in the management of pulmonary tuberculosis. As in the case of the iodides, there are more failures recorded for thymol than there are successes, so that today these indifferent results have placed this drug on the discard list. The sulfonamides and penicillin are now generally the antibiotics of choice. These drugs can be used singly or together as the case may require. Although x-ray therapy has been shown to produce no specific effect on the actinomycete itself, there have been many reports in the literature of beneficial effects resulting from this method of treatment. It is suggested that the fibrous reaction resulting from irradiation may incarcerate the causative organisms and consequently explain the good results recorded for this agent in the arrest of the disease. The importance of surgery in conjunction with any of the above therapeutic measures has been recognized generally. As emphasized by Wangensteen,[1] the infection being an anaerobic one demands the removal of dead tissue which is poorly oxy-

genated and, accordingly, produces a favorable culture medium for the propagation of the Wolff-Israel actinomyces.

Modern therapy of actinomycosis takes into consideration initially the general condition of the patient. The importance of improving the patient's depleted condition, as a factor in arresting the progress of the infection and increasing his tolerance to direct and more extensive surgical procedures, has ben ably emphasized by Gage, Lyons and DeCamp.[3] Lyons'[6] fundamental contributions to the preparation of the chronically ill patient for surgery represents an advance deserving of special mention. As pointed out by these authors, multiple transfusions are effective in correcting the anemia and reduced circulating blood volume in patient's chronically ill with actinomycosis. Likewise, a proper high-vitamin, high-protein dietary is of great importance. The regular meals should be supplemented by high protein in-between-meal drinks prepared with any one of several acceptable protein powders now available. Attention should be directed to the observation of Miller, Robscheit-Robbins and Whipple[7] which reveals that the chief reserves of protein are in body cells. In patients depleted of this reserve as a result of chronic infection and associated malnutrition there develops a severe anemia. As Gage, Lyons and DeCamp[3] have observed, multiple transfusions are required to correct the anemia as the quantity of proteins which would have to be ingested and assimilated by the body to correct these variations from the normal protein balance would be so great as to be impossible in many of the more serious cases. Readjustment of the blood volume and correction of the anemia permit wound healing to progress and then re-establishment of cellular reserves of protein.

In the regimen designed to improve the general condition of the patient should be included the administration of an acceptable intravenous vitamin preparation. This seems to stimulate appetite and furnishes necessary substances for wound repair.

Inasmuch as penicillin produces few toxic reactions and is considered safer than the sulfonamides, this is the drug of choice as the antibacterial agent during initial treatment and hospitalization. A dosage of 25,000 to 50,000 units every two or three hours is acceptable, but there is no objection, and, in serious cases, it is perhaps desirable to employ larger dosages of 100,000 to 200,000 units of the drug at three hour intervals. Sulfonamides may be used in the ambulant patients whose condition is not so serious as to require hospitalization. Moreover, this drug may be used to advantage as a continuing form of antibiotic therapy in patients who have been hospitalized and are then allowed to return home. With the supportive measures considered above, serious cases of actinomycosis can now be placed in optimum condition to stand surgical excision of devitalized tissue and the proper curettage of extensive fistulous tracts. In the less serious cases in which important viscera are uninvolved, drainage of abscesses and the curettage of draining tracts may be all that is required in the way of surgery. The patient should be informed of the resistant nature of the disease and advised at the time of discharge to return at the first sign of any recurrent infection, so that energetic treatment can be recommenced. In the more serious thoracic and abdominal lesions, extensive surgery may be required if the above more conservative measures fail to arrest the disease. Procedures must be designed and selected to fit the given case in order to achieve the desideratum noted above, namely, the removal of devitalized tissues and the eradication of anaerobic retreats for the causative organism.

CONCLUSION

In closing, we would like to emphasize that actinomycosis is still a problem disease, carrying with it a grave prognosis in cases of any significant extent. Careful repeated follow-up examinations are of importance in all cases. Although cervicofacial actinomycosis presents a much happier prognosis than do the pleuropulmonary or abdominal types, its therapy should be nonetheless assiduous, for this condition has potentialities of becoming as serious a problem as

either of the other types if not adequately arrested. The early recognition of the disease before it extends to involve important adjacent viscera, and energetic surgical therapy as outlined above, with the support of antibiotics administered over an adequate period of time, represent the most acceptable means today of arresting this disease.

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DISCUSSION

Dr. Mims Gage (New Orleans): I wish to thank Dr. Holcombe for presenting this paper before us. He has dramatically delineated the newer aspects of treatment of an old disease.

Dr. Holcombe's plea for early diagnosis before actinomycosis has involved important structures and fascial planes is worthy of close scrutiny by all of us. As was stated by the essayist, if the patient is seen early and given intensive treatment, not only can complications be prevented but the disease can be completely eradicated. Chemotherapeutic and antibiotic agents in large doses have cured patients who have exhibited all the complications that this disease produces.

There are three types of actinomycosis, i. e., the lumpy jaw, abdominal (ruptured appendices) and pulmonary. They rapidly produce the complications that were enumerated by Dr. Holcombe. I would like to emphasize what he has told us about restoring the blood volume, circulating hemoglobin, and red cell mass. Drs. Lyons, DeCamp and myself pointed out several years ago that there is a need for restoring the plasma protein, blood volume, hemoglobin, and circulating red cell mass before improvement can be demonstrated. Therefore, the basal metabolic level should be restored to as nearly normal as possible before intensive treatment is instituted.

Dr. Isadore Dyer, a former Professor of Dermatology and Dean of the Tulane Medical School, told us in 1915 that chronic syphilitics should never be treated until the patient's anemia has been overcome if he is to be cured. Today Dr. Holcombe has demonstrated the wisdom of that statement as applied to patients with actinomycosis.

CHORIONEPITHELIOMA

E. E. DILWORTH, M. D.
C. R. MAYS, M. D.
AND
L. A. HORNBUCKLE, M. D.
SHREVEPORT

The infrequency of chorionepithelioma makes it unlikely that the average doctor would encounter a case in many years of private practice. However, there is no rarity of reports of this tumor in the medical literature. These reports often show a marked variance in the course and mortality of the condition.[1]

We have reviewed 9 cases from the records of Shreveport Charity Hospital. Two other cases were studied from the Pathology Department of the hospital. These were cases in which specimens were sent in for study and diagnosis. The private physicians have kindly allowed the presentation of these cases here.

Ewing's classification[2] of chorionepithelioma has been used and all 11 of these cases come under the heading of choriocarcinoma. Microscopically these tumors were recognized by the wild growth of masses of trophoblastic cells invading the uterine muscle with destruction of tissue and liberation of blood in tissue spaces. Chorionic villi were not seen in any of these cases. All cases were classified by Dr. W. R. Mathews of Shreveport Charity Hospital.

Synctioma and chorio-adenoma destruens are also considered as varieties of chorionepithelioma by Ewing. The failure to classify properly these less malignant types of chorionepithelioma is the most likely explanation for the differences in mortality seen in the various reports of this tumor. A chorionepithelioma registry, headed by Dr. Emil Novak, has been established to

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(From the Department of Obstetrics and Gynecology, Shreveport Charity Hospital.)

make uniform classification of these tumors possible and to aid the profession in treatment of individual cases.

The fatal outcome of our cases was no doubt hastened by the delay between the appearance of symptoms and the establishment of diagnoses. This time varied from two months to two years. The responsibility for this delay is about equally shared by the patient and the doctor.

There was only one case in which a careful search for metastatic lesions revealed none present before the time of operation. It is likely that small, unrecognizable metastatic lesions were present in the lungs of this patient because they were easily demonstrable one month after operation. We think this lends strength to Hertig's suspicion that the malignant process may be under way even before the responsible pregnancy has been expelled from the uterus. Douglas and Otts have reported an undoubted case of this type.[3]

Metastasis.—In a study of the autopsies which were done on 8 of the 11 patients metastatic lesions were found in the following organs: lungs, liver, vagina, brain, kidneys, bladder, urethra, ovary, skin, regional nodes, ileum, jejunum, large bowel, spleen and meninges.

Curettement.—The danger of dilatation and curettage in causing spread is somewhat theoretical and will be difficult to prove. However, we have ample proof that the method is fallible as a diagnostic procedure. In this choriocarcinoma group four curettements were done. One of the four failed to reveal diagnostic tissue because the tumor mass was deep in the wall of the uterus.

From autopsy findings it is evident that in at least 5 of the 11 cases D&C would have been of no help in diagnosis. Two of these had the tumor in the tube. In 3 others the lesion was deep in the uterine wall and not accessible to the curette.

Biologic Tests.—The biologic tests for pregnancy are likewise not infallible as a diagnostic method in these cases. This is especially true of the spinal fluid Friedman test. One of the cases had repeated positive urinary Friedman's, but failed to show a positive spinal fluid Friedman with 10 cc. of spinal fluid even when the patient was riddled with metastatic lesions.

Another case gave a positive Friedman test three times. The spinal fluid was positive before removal of the uterus than became negative after operation. The urinary Friedman, on the other hand, remained positive after removal of the uterus, tubes, and ovaries and this was before any metastic lesions were demonstrable. This, in a rough way, indicates that the spinal fluid Friedman test is a poor substitute for the quantitive Friedman. The amount of tumor tissue required to produce enough of the hormone to give a positive biologic test does not appear to be comparable in any two cases.

The biologic test is a definite aid in diagnosis but as Park and Lees[4] emphasize, it must be interpreted in the light of the clinical findings.

Lutein Cysts.—Lutein cysts were palpable in only one case. Three cases showed gross enlargement in the pathological specimen or at autopsy. No record of microscopic lutein cysts was made. The ovaries should not be removed because of the presence of these benign cysts that may accompany chorionepithelioma or hydatidiform moles.

Symptoms.—The presenting symptom was abnormal and excessive bleeding in 9 of the 11 cases. This bleeding varied from a prolonged bloody discharge to an exsanguinating hemorrhage. The 2 cases which did not have abnormal bleeding as a chief complaint complained of abdominal pain. One of these had chills and fever apparently due to a complicating pelvic cellulitis. All patients except 1 had some abnormal bleeding and that one had the tumor in her tube.

Cause of Death.—The cause of death in these patients varied with the type of metastasis. The 2 most unusual deaths were from rupture of the liver at the site of metastasis with fatal hemorrhage into the abdominal cavity.

Type of Preceding Pregnancy.—Another different and interesting finding in this

series was that only 3 of the choriocarcinomas followed hydatidiform mole. Of the remaining 8 cases, 3 followed abortion, 3 followed full term pregnancy and 2 followed tubal ectopic pregnancy. This serves as a reminder that chorionic malignancy may develop anywhere a pregnancy can develop. It is true that in general 50 per cent of chorionepitheliomas follow hydatidiform mole but this figure cannot be taken too literally in considering individual cases or small series.

DISCUSSION

It is our feeling that careful classification of these tumors by a competent pathologist is of the utmost importance. The realization that the synctioma and chorio-adenoma are rarely a threat to the patient's life should give confidence to observe the patient who shows a positive Friedman test one to three months after the passage of a hydatidiform mole. On the other hand, little will be lost should the case prove to be the more rare choriocarcinoma since it is almost uniformly fatal by the time it has grown to the point of recognition. Many uteri must have been sacrificed with the hope of curing choriocarcinoma while it was early when actually a true malignancy was never present.

The use of x-ray in our experience has been very disappointing. In almost every case the tumor "grows in the ray" and usually metastatic legions have not been reduced by this treatment regardless of how accessible the lesion might be.

Some may question the decision to do a hysterectomy in these patients with choriocarcinoma who already show metastasis. We have operated on these patients with no hope of the metastatic lesions regressing after removal of the parent tumor, although it did temporarily occur in one case. However, surgery does prolong the life somewhat by preventing early death from uterine hemorrhage. It also prevents the severe secondary anemia which would make the patient liable to early death by intercurrent infection. That is about all that our treatment has accomplished in this malignant group. A more detailed report of these cases has been made elsewhere.[5]

SUMMARY

1. Eleven cases of choriocarcinoma are presented with mortality of 100 per cent.

2. X-ray is of little or no value in treating choriocarcinoma or its metastatic lesions.

3. The presence of metastasis is no contraindication to surgery.

4. A better understanding of these tumors will be possible if every doctor who encounters a case of this type will submit his surgical specimens to the Chorionepithelioma Registry.

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DISCUSSION

Dr. R. E. C. Miller (Alexandria): Dr. Dilworth has just presented an excellent paper on chorionepithelioma, a paper prepared by him, Dr. C. R. Mays and Dr. L. A. Hornbuckle of Shreveport, Louisiana. In this paper they discussed 11 cases of chorionepithelioma.

Many of us, probably the great majority of us, have never seen a patient with chorionepithelioma, but all of us have heard at one time or another, that this tumor is the most malignant one that a gynecologist and obstetrician might encounter.

At least it certainly is a fatal carcinoma as definitely demonstrated by Dr. Dilworth; yet, in the literature, there are many reports of cures of chorinonepithelioma. But, I prefer to accept the results that Dr. Dilworth has reported, for I believe he has given a better classification of the tumors of the chorion, namely, choriocarcinoma, for the trully vicious malignant cancer of the chorion. And then he divided them further into the syncytioma and the chorio-adenoma and these are the least malignant or killing. People who suffer with these two latter condition have a good prognosis with proper treatment.

When one would review the literature on chorionepithelioma, one is certainly impressed with the various incidences of chorionepithelioma and one is impressed with the various percentages given as to the incidence of chorionepithelioma following a hydatid mole, and further the incidence following any pregnancy or any abnormal pregnancy.

It was interesting to me to determine how many births occurred in Alexandria, Louisiana, during the past five years and I learned that there were

approximately 13,000. No figures were available to me, to determine how many pregnant women were admitted to the hospitals situated in our community, nor were any records available to determine how many abortions occurred in these hospitals; however, it is interesting to report that there were only nine "moles" reported and recorded and there was only one chorionepithelioma diagnosed and reported. Jefferys and Graffagnino reported on a large series of pregnant women admissions to Charity Hospital in New Orleans. They stated that the incidence of mole was 1 to 3,049, whereas in Alexandria, the incidence of mole was 1,333. There are many variants of incidences of mole and chorionepithelioma as these figures indicated.

Remarkably, the chorionepithelioma reported in our area, occurred in a nine year old negro girl, who gave no history of pregnancy; simply a history of vaginal bleeding and an abdominal tumor mass. This child was operated upon by me and a six pound right ovarian tumor was removed, together with all of the internal genital organs. A diagnosis of chorionepithelioma of the ovary was made by the hospital pathologist and this diagnosis was confirmed by another pathologist. It is further interesting to note, that this case presented a biological picture usually seen in chorionepithelioma, namely, a positive Friedman and the left ovary contained lutein cysts. The uterus showed no signs of a previous pregnancy. This child lived only a few weeks. Our only explanation is that this chorionepithelioma was probably an embryonal rest, and a few cases reported in very young girls gives us no better explanation.

As Dr. Dilworth stated, do not think that the Friedman or any other biological tests are infallible. They are a help, definitely, but, Frank has demonstrated that 0.0025 cc. of urine from a hydatid mole gave a positive Friedman reaction, while a chorionepithelioma with metastasis required 10 cc. of urine to obtain a positive Friedman reaction. At the Charity Hospital in Pineville, Louisiana, we have had similiar experiences with quantitive Friedman tests. I remember particularly a case in which a very high dilution of spinal fluid gave a positive Friedman test and we thought that we were dealing with a mole or chorionepithelioma. In reality this case proved to be of twins. And, too, there are many cases reported in literature of a proven chorionepithelioma with a negative Friedman reaction.

Lutein cysts that accompany hydatid mole or a chorionepithelioma will at times present a very baffling decision for you to make. To those of you who have never seen these lutein cysts, a word of caution, do not succumb to the temptation to remove these tumors, even though your judgment will be taxed to the utmost, for usually these lutein cysts disappear shortly after the removal of the mole.

I, too, make the plea that to those of you who encounter a case of chorionepithelioma report your history and surgical specimen to the Chorionepithelioma Registry of the Association of Gynecologists, Obstetricians and Abdominal Surgeons.

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RENEWAL OF PRESCRIPTIONS

The matter of the refilling or renewal of prescriptions by pharmacists is becoming one of acute legal concern. This information will probably be received by most physicians with some surprise. As the public well knows, prescriptions have been refilled as a matter of custom, except those containing narcotic drugs, potent drugs, or those which have been designated by the physician as not to be refilled.

In a widely circulated address before the National Association of Retail Druggists, Commissioner Paul B. Dunbar insisted that no prescription should be refilled except by the will and purpose of the prescribing physician, which must be attested in writing. In the *American Druggist Blue Book 1950*, there is an article consisting of twenty-two questions and answers. The questions were put to the Food & Drug Administration by the American Druggist, and the answers are printed as given by the Food & Drug Administration. In this catechism a prescription is defined by the F.D.A. as a written expression of the physician's will and purpose that the patient be furnished with a specific quantity of a drug for use as a physician directs. The refilling without his authorization is forbidden. It is stated, by way of further explanation, that the physician may, except with narcotics, direct as many refills as he may wish. The American Druggist asks the question:

"By its position on refills, is the F&DA injecting itself into the traditional doctor-pharmacist-patient relationship? Is it trying to regulate the practice of medicine?"

The answer is given as follows by the Food & Drug Administration:

"No—neither! The law's ban on non-authorized refills about which the doctor knows nothing should really strengthen and dignify the professional relationship between the doctor and the pharmacist. Far from demoralizing prescription practice, it emphasizes the pharmacist's professional rather than commercial interest in the welfare of the patient. It should bring the pharmacist into closer contact with his fellow professionals in the health field. It emphasizes the professional responsibility of the doctor in writing prescriptions and the pharmacist in filling them. It makes certain the patient gets no more medication than the doctor intended."

In this connection, the recent action of the American Pharmaceutical Association is of great interest. They feel that since there has been no regulation and no directive issued by the Food & Drug Administration, but only an opinion voiced by the Commissioner, that further clarification of the matter from a strictly legal standpoint is necessary. As a result, the American Pharmaceutical Association has engaged eminent counsel, the firm of Arnold, Fortas & Porter. Acting through this counsel, the Association has petitioned the Food & Drug Administration to hold a hearing in order

that the matter may be thoroughly investigated and clarified. It is stated in the petition that there is no justification in the law as written for the position taken by the Food & Drug Administration, and that the law, in the wording, supports the opposite contention, namely, that such prescriptions as do not contain potent drugs or narcotics, or have not been marked not to be refilled by their physicians, are exempt from the action of the law and refilling is permitted. It is pointed out that no legal action has been taken against a druggist for the matter of simply a refill, and that probably the Food & Drug Administration is unwilling to risk a test in court of the law on this point. It is stated that evidence gathered by the American Pharmaceutical Association indicates that the Food & Drug Administration is attempting to secure conformity of the profession to the unofficial views of the Commissioner without recourse to a formal mandate. In turn, the pharmacists under the hazard of possible prosecution must live up to what the officials insist is the meaning of the law. The request of the counsel for the American Pharmaceutical Association was to call for a hearing and to place the hearing in the first part of October. It seems probable that whatever conclusion is reached by the Food & Drug Administration will take the form of a directive or mandate. It is also probable that such an action on the part of this bureau will utimately have to be supplemented by a change in the law to support the F.D.A.'s position. It is at this point that the interests of the medical profession become involved.

If the Food & Drug Administration grows as much in authority and influence in the next twenty-three years of its existence as the Department of Internal Revenue has grown in its thirty-three years, it will be an easy matter for every conceivable phase of the practice of medicine to be administered by directive from Washington. There is also another point for consideration: Decision as to whether prescriptions of the type under discussion should be refilled or not refilled is one which should be arrived at by mutual adaptation on the part of the medical and pharmaceutical professions to the best interests of the patient and not by the interjection of commands by a bureaucratic authority.

Organized medicine should reflect on the potentialities of the situation and should be prepared to present its case clearly when the hearing is called.

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DIABETES DETECTION CAMPAIGN

During the week of November 12-18, 1950, the American Diabetes Association will direct and manage a diabetes detection drive, the object of which is to uncover as many as possible of the hidden diabetics throughout the nation.

The Association points out that during last year's campaign, which was the second year in which this had been attempted, there were approximately 7500 hidden diabetics discovered. It is hoped in the campaign of the present year, with the new approval of self-testing by the A.M.A., and with much wider cooperation by business and industry in the drive that there will be an improvement on last year's record. There are good reasons to believe that there are a million hidden diabetics in the United States. They state also that there are approximately another two million people who are likely to develop diabetes as they grow older. A recent survey of a community, in which the investigation was carried out with all possible thoroughness, showed that there was approximately one hidden diabetic for every known diabetic under treatment.

It is also of interest to note that in 1900 diabetes ranked twenty-seventh among the causes of death, and in 1945 it had become eighth among diseases as a cause of death. Some of this increase was due to the fact that more diabetes was being diagnosed. It is natural to think also that some of this increase was due to the increase of approximately eighteen years in life expectancy between 1900 and 1945.

As all physicians will recognize, the problems of diabetes are treated more successfully the earlier the condition is discovered.

Physicians, accordingly, have every reason to cooperate in the diabetes detection drive, and to assist wherever possible in advising and working with any of the units in their community that are making an effort to uncover the hidden diabetic. It is reported that the plans of the Association include the circularizing of the members of the profession, and securing the cooperation of large groups of employers, both in business and in industry. It is to be hoped that the members of the profession will give every cooperation.

ORGANIZATION SECTION

The Executive Committee dedicates this section to the members of the Louisiana State Medical Society, feeling that a proper discussion of salient issues will contribute to the understanding and fortification of our Society.

An informed profession should be a wise one.

MORE DATA REGARDING MEDICAL MILITARY SERVICE

In the September issue of the New Orleans Medical & Surgical Journal, we carried up-to-date information in regard to the participation of our doctors in the present emergency. The activities of our organization have been developed along the lines as indicated in that article. However, since this has been published, we feel that it would be most interesting to the doctors of our state to learn that the recent passage of Senate Bill 4029 may alter somewhat the modus operandi in the selections of medical officers for the Army, Navy, and Air Corps. Senate Bill 4029 was signed by the President on September 9.

"WHO MUST REGISTER? Physicians and dentists *who have not reached the age* of 50 and are *not members of military reserves.* Veterinarians, optometrists, pharmacists, osteopaths and/or other specialist categories if specified by the President. (Law specifically states that it does not apply to military reserves; they are already subject to military orders.)

"WHO ARE ELIGIBLE FOR DRAFT, AND IN WHAT ORDER WILL THEY BE CALLED? Any registrant (above) is subject to induction if acceptable to the military. The law provides that registrants will be called up on the following priority:

1. Former ASTP and V-12 men who have *not served on active duty* (military, Coast Guard or Public Health Service) and others *deferred from service to continue their education* during World War II, and who have had less than 90 days of active duty (military, C. G., or PHS).

2. Members in the above groups who have had more than 90 days active duty (military, C.G., or PHS) but *less than 21 months.*

3. With no reference to above groups, those who did not have active service, (military, C.G., or PHS) subsequent to September 16, 1940; this could include postwar medical graduates as well as other physicians who have not served and have not reached their 51st birthday.

4. All others, including World War II non-reserve veterans. Men in this group to be called on basis of extent of duty; those with least duty first, etc.

"WHEN WILL DRAFT TAKE EFFECT? Not until the President sets a time for registration. Nothing official, *but registration deadline probably in next few weeks.* Men will register at "appropriate points of registration" in community. After registration, Selective Service will place the man in one of four classes listed above. Then, if to be called, he will be ordered up for his physical. Following this, 21 days to set affairs in order before reporting to Armed Forces Induction Station. Subsequently he will be offered a commission and assignment to a service.

"CAN REGISTRANT GET RESERVE COMMISSION? Yes, if acceptable to military. If the man applies for and is granted a reserve commission, he will come under military orders and Selective Service will not process him further.

"WHO GETS THE $100 PAY BONUS? Every reserve officer called to duty, on voluntary or involuntary basis, receives the extra $100 per month. Men required to register under this act also may qualify for the $100—but only if they vounteer prior to their actual induction.

"WHO IS ELIGIBLE FOR DEFERMENT? Actual deferment is at the discretion of local Selective Service boards. However, the law states that "the President is authorized to provide for" certain deferments. Action under this clause would be based on the registrant's previous military service, his dependency status and any undue hardship that might ensue.

"WILL PROFESSION ADVISE SELECTIVE SERVICE ON MEN TO BE CALLED? Yes. The law provides for establishment of a National Advisory Committee "which shall advise SS system and coordinate work of state and local volunteer advisory committees with respect to selection of needed . . ." professional personnel. Committee will be composed of men "outstanding in medical, dental and allied services." *Medical and dental professions must be represented on the National Committee,* but representation of other professions not required. Law does not control advisory committees; whether these are established and made effective depends on local conditions.

"WILL DRAFT CREATE CRITICAL DOCTOR-SHORTAGE AREAS? Conceivably it might. But law itself attempts to set up safeguards. It says the National and state and local committees shall *"give appropriate consideration to" civilian as well as military medical and dental requirements.* Another section underscores this policy: "Maintenance of national health, safety or interest" should be considered in granting deferments. In calling up reserves, *Army commanders* also under orders to give careful consideration to doctor-shortage areas.

"HOW MANY WILL BE DRAFTED? Military medical officers hope enough men now will volunteer to meet requirements. They are prepared to use law's authority for mandatory inductions, but are confident that these cases will be rare. They are hopeful that the $100 bonus, which is denied to men involuntarily inducted under this act, will attract registrants to volunteer.

"OTHER PROVISIONS: One section of law authorizes transfer of medical officers from one service to another, with consent of the officer and of services involved. Officer protected in promotion, retirement and pay . . . Another provided that any persons who have served in armed forces or PHS after September 16, 1940, and is recalled, may be "promoted to a grade commensurate with his education, experience and ability." . . . Law states "it is the sense of Congress" that Selective Service deferments will be granted to premedical, predental and allied students in numbers equal to the present such enrollment. This ruling more or less formalizes present Selective Service policy and sets a total figure for deferments in each professional category . . . Inductees under doctor-draft required to serve *21 months* . . . Anticipation is that Advisory Committees will operate like Procurement and Assignment of World War II . . . Bonus of $100 now goes to all reserves, whether called up voluntarily or involuntarily; on this Congress reversed comptroller general, who had ruled that reserves called up involuntarily not eligible . . . Doctor-draft law, an amendment to Selective Service Act, *expires with that law next July,* unless extended by Congress."

During the last World War the doctors of our state exceeded their quota by 114%. Many of the physicians who were in service left behind them large practices and as a result there was a considerable handicap on the civilian population. It is felt that with the record which we have established in this state, and the great need for medical officers in the military service every one of us will be prompted to take an inventory of the possibility of serving in this emergency.

The Louisiana State Medical Society is giving its 100 per cent cooperation to our military services, and we anticipate the greatest understanding and cooperation among the doctors of our state.

LOUISIANA STATE MEDICAL SOCIETY NEWS

CALENDAR

PARISH AND DISTRICT MEDICAL SOCIETY MEETINGS

Society	Date	Place
East Baton Rouge	Second Wednesday of every month	Baton Rouge
Morehouse	Third Thursday of every month	Bastrop
Natchitoches	Second Tuesday of every month	
Orleans	Second Monday of every month	New Orleans
Ouachita	First Thursday of every month	Monroe
Rapides	First Monday of every month	Alexandria
Sabine	First Wednesday of every month	
Second District	Third Thursday of every month	
Shreveport	First Tuesday of every month	Shreveport
Vernon	First Thursday of every month	

SECTIONAL MEETING OF THE AMERICAN COLLEGE OF SURGEONS

A Sectional Meeting of the American College of Surgeons will be held in St. Louis on January 22 and 23, 1951, with headquarters and the program at Hotel Statler. Members of the College of Surgeons are invited and also any other doctors who wish to attend. There probably will be a registration fee of $5.00 for non-members.

The states covered are Missouri, South Dakota, North Dakota, Minnesota, Wisconsin, Iowa, Kansas, Louisiana, Arkansas, Mississippi, Illinois and Indiana. An excellent and practical program has been arranged. There will be an extra day of operative clinics besides the scheduled days.

Chairman is James Barrett Brown, M. D., Grand Avenue and Olive Street, Saint Louis 3. Further details will be announced later.

IDENTIFICATION CHART OFFERED FOR RUBBER GLOVES

The Seamless Rubber Company has had prepared and is offering to send to hospitals, at no cost, a color chart showing the various colors used to band "KOLOR-SIZED" Seamless Standard Surgeons' gloves. The cardboard chart measuring 11 inches by 14 inches is printed in five colors indicating the color used for each size. Designed to hang in Operating Room, Sterilization and Glove Sorting Room walls in hospitals and in surgeons' offices, it tells at a glance the size indicated by the colored band—to aid the nurse in matching gloves before sterilization. The reverse side of the chart is printed with an approved procedure for sterilizing surgeons' gloves. The chart will be mailed immediately, without cost, upon request to The Seamless Rubber Company, New Haven, Connecticut.

L. S. U. WILL HAVE REGULAR RADIO PROGRAMS

Louisiana airwaves will be carrying three new service programs, starting Sept. 17, when WNOE begins a series of broadcasts from Louisiana State University.

All programs will originate live at WLSU, the University's FM station, and be aired to the entire state and parts of neighboring states through the 50,000-watt AM power of WNOE in New Orleans, 1060 on the dial.

A voice of general interest will be a Sunday half-hour program at 1:00 p. m., titled "L. S. U. Speaks." This series will be initiated Sept. 17 by L. S. U. presidest Harold W. Stoke, speaking on the subject of "What can we hope from education?" Key University officials will talk on following broadcasts on subjects ranging from "Atoms, friends or foes?" to "How many should go to college?"

EENT OFFICE AND EQUIPMENT AVAILABLE

Office and equipment of eye, ear, nose and throat specialist, who recently died, available. No other physician in this specialty within a radius of 35 miles. For further information contact Mrs. D. T. Martin, Donaldsonville (telephone 643).

GENERAL PRACTITIONER NEEDED

Doctor needed to serve Albany, Holden, Doyle and Livingston, Louisiana. Doctor's office and drugstore available in Albany. Contact Mr. Sam Berey, P. O. Box 63, Albany, for further information.

NEW NATIONAL FORMULARY IX NOW AVAILABLE

The Council of the American Pharmaceutical Association has announced publication of the Ninth Edition of the *National Formulary*, which is one of the official compendia for drugs under the provisions of Federal and State Food, Drug, and Cosmetic Laws.

In describing the new edition in the *Practical Pharmacy Edition of the Journal of the American Pharmaceutical Association* for July, Dr. Justin L. Powers, Chairman of the A.Ph.A. Committee on *National Formulary*, points out that surveys were made of the extent of use of *National Formulary* drugs at the beginning of the revision period. In these surveys, information was furnished by practicing pharmacists who were given a list of the drugs official in *National Formulary VIII* and asked to indicate the extent of their use, based upon their experience in prescription compounding and other demand for such drugs.

Therapeutic value of the drugs in use was also

determined by the Committee of Revision, prior to selecting the drugs to be included in *National Formulary. IX.*

DEATH OF DR. JAMES L. KNOLL, JR.

Dr. James Lyle Knoll, Jr., 34, of Bunkie, died at his home Friday night, August 24, of a coronary occlusion after seeing patients all day at his Knoll-Temple Clinic.

The young physician, who with his partner, Dr. H. G. Temple, operated the clinic and the Knoll Infirmary, came to Bunkie in 1944 from Pineville, where he was superintendent and chief surgeon at the State Colony.

He was born in New Orleans on September 26, 1915, and attended grammar school at Catholic High in Baton Rouge. He graduated from high school at St. Stanislaus College, Bay St. Louis, Miss., in 1933. In 1940, he was graduated from the L. S. U. School of Medicine. After graduating from L. S. U., Dr. Knoll interned at French Hospital in New Orleans and Highland Sanitarium in Shreveport. In 1942, he was commissioned a Lieutenant, j.g. in the Navy.

Surviving Dr. Knoll are his widow, Mrs. Frances Johnston Knoll, and three children, Diane, 8, James Lyle, III., 6, and Martha Frances, 7 months. Also surviving are his parents, Mr. and Mrs. J. L. Knoll, Sr., who recently moved to Bunkie from Mobile to be near their only son.

Physicians from throughout central Louisiana attended the funeral, which was held Saturday afternoon at St. Anthony's Catholic Church in Bunkie. Interment was in the Pythian cemetery in Bunkie.

Dr. Knoll was, at the time of his death, president of the Eighth District of the American Academy of General Practice and was a past president of the Avoyelles Parish Medical Society.

ANNOUNCEMENT OF VAN METER PRIZE AWARD

The American Goiter Association again offers the Van Meter Prize Award of Three Hundred Dollars, and two honorable mentions, for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Columbus, Ohio, May 24, 25 and 26, 1951, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English; and a typewritten, double-spaced copy in duplicate, sent to the Corresponding Secretary, Dr. George C. Shivers, 100 East Saint Vrain Street, Colorado Springs, Colorado, not later than March 1, 1951. The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award Essay by the author, if it is possible for him to attend. The essay will be published in the annual Proceedings of the Association.

FOURTH CLINICAL SESSION OF THE AMERICAN MEDICAL ASSOCIATION

The Fourth Clinical Session of the A.M.A. will be held in Cleveland, December 5-8, 1950. Dr. Lull says it will be the best ever scheduled.

The program incorporates constructive suggestions which have been made by general practitioners who have participated in the previous sessions.

Those planning to attend should inform themselves carefully of the arrangements.

Each clinical session will be limited to an attendance of 100 physicians. These small groups will make it possible for the general practitioner to enter actively into the discussion and to inquire about his own cases. Leading men in each of the fields under discussion will be available to help with the problems presented.

Because of the unusual interest displayed last year in the section devoted to management of heart cases, there will be a similar session this year. It will include discussions on hypertension, recent advances in drug therapy, including ACTH as it applies to heart disease, acute arterial occlusion and cardiac arrhythmias.

The steadily climbing registration of general practitioners at the clinical sessions and the comments of those participating indicate these meetings are valuable means of keeping abreast of developments in medicine. It is hoped that a record number of physicians will take advantage of the opportunity in December to attend. The program has been designed with that in mind.

VOLUNTARY HEALTH INSURANCE PLANS

In the September issue of the Journal, a typographical error was made on page 135. The last sentence of the third paragraph should read: "During the first quarter of 1950, all Blue Shield Plans collected $37,478,306, and returned to the doctors of this nation in the form of medical-surgical payments $30,384,399, or 81.07 per cent of the total income."

COURSE IN GENERAL MEDICINE

Orleans Chapter, American Academy of General Practice, in cooperation with the Louisiana State University School of Medicine, is offering a course in medicine as applied to general practice for any interested physicians who are members of their respective State and Parish Societies.

Two hour sessions will be held each Wednesday night at 8 P. M. beginning October 18, 1950, for a period of twenty-five weeks. Minimum number of registrants, thirty, and maximum, seventy-five.

Due credit and number of hours will be given to any one taking this course. Address all inquiries to the Registrar, Mrs. Vivian Johnston, Louisiana State University School of Medicine, 1542 Tulane Ave., New Orleans.

The members of Orleans Chapter, American Academy of General Practice, welcomes any member of organized medicine to participate in this course.

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WOMAN'S AUXILIARY OF THE LOUISIANA STATE MEDICAL SOCIETY

LAFAYETTE PARISH

The Woman's Auxiliary to the Lafayette Parish Medical Society held its July meeting at the home of Mrs. Edward M. Harrell, with Mrs. Stanley E. Morgan as cohostess. Following the business meeting, luncheon was served.

There was a meeting of the Lafayette Parish auxiliary at the home of Mrs. William Melancon in Carencro, with Mrs. Douglas Chesson as hostess, and presided over by Mrs. Edward Wynne, President.

The Woman's Auxiliary to the Lafayette Parish Medical Society, at a meeting in the home of Mrs. Thomas Latiolais, Jr., with Mrs. T. A. Kimbrough as cohostess, voted to donate $500.00 to the Lafayette Parish Cancer Society.

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WOMEN'S AUXILIARY TO THE SOUTHERN MEDICAL ASSOCIATION

The Woman's Auxiliary to the Southern Medical Association will hold its twenty-sixth annual meeting at the Hotel Jefferson, St. Louis, November 12-16, 1950.

The members of the State Auxiliary are urged to attend and make this the biggest and best meeting in the history of the Woman's Auxiliary to the Southern Medical Association. Our well loved president of the Woman's Auxiliary to the A. M. A., Mrs. A. A. Herold of Shreveport, and our equally well loved president of the State auxiliary, Mrs. DeWitt T. Milam of Monroe, will appear on the program, which tentatively is as follows:

Monday, November 13th

10:00 A.M.—Registration

Tuesday, November 14th

8:00 A.M.—Executive Board Breakfast

10:00 A.M.—General Session
- Addresses of Welcome
- Response
- Recognition of Guests
- Reports of Officers
- Memorial Service

2:00 P.M.—Fashion Show and Tea, honoring Mrs. Arthur A. Harold, President Women's Auxiliary to the A. M. A.

7:00 P.M.—Dinner and Entertainment with Southern Medical Association

Wednesday, November 15th

10:00 A.M.—General Session (continued)
- Reports of Committees
- Reports of Councilors
- Election and Installation of Officers

1:00 P.M.—Luncheon

Guest Speakers:
- Dr. Elmer Henderson, President, American Medical Association
- Mrs. Arthur A. Herold, President, Women's Auxiliary to the American Medical Association

Recognition of State Presidents and Councilors

Adjournment

Mrs. George D. Feldner, Louisiana Councilor, Woman's Auxiliary to the Southern Medical Association.

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PUBLICATIONS RECEIVED

Bruce Publishing Company, Saint Paul: Cerebral Palsy, by John F. Pohl, M. D.

Philosophical Library, N. Y.: Freud: Dictionary of Psychoanalysis, edited by Nandor Fodor and Frank Gaynor.

Henry Schuman, Inc., Publishers, N. Y.: Immortal Magyar: Semmelweis, Conqueror of Childbed Fever, by Frank G. Slaughter, M. D.; Sir William Osler Aphorisms, collected by Robert Bennett Bean, M. D., and edited by William Bennett Bean, M. D.

Superior Publishing Company, Seattle: Doctor Come Quickly!, by Frank J. Clancy, M. D.

Charles C Thomas, Publisher, Springfield, Ill.: The Esophagus and Pharynx in Action, by William Lerche, M. D.; Significance of the Body Fluids in Clinical Medicine, by L. H. Newburgh, M. D.; The Clinical Use of Radioactive Isotopes, by Bertram V. A. Low-Beer, M. D.; Carbon Dioxide Therapy, by L. J. Meduna, M. D.; Post-Graduate Lectures on Orthopedic Diagnosis and Indications, by Arthur Steindler, M. D.; Cancer of the Colon and Rectum; Its Diagnosis and Treatment, by Fred W. Rankin, M. D., and A. Stephens Graham, M. D.